

METHODS OF TREATING ALZHEIMER'S DISEASE  
USING ARYL ALKANOIC ACID AMIDES

5        This application claims priority to U.S. Provisional  
Application Serial No: 60/387,880, filed June 11, 2002.

Field of the Invention

10        The present invention relates to the treatment of  
Alzheimer's disease and other similar diseases, and more  
specifically to the use of compounds that inhibit beta-  
secretase, an enzyme that cleaves amyloid precursor protein to  
produce A beta peptide, a major component of the amyloid plaques  
found in the brains of Alzheimer's sufferers, in such methods.

15

Background of the Invention

Alzheimer's disease (AD) is a progressive degenerative  
disease of the brain primarily associated with aging. Clinical  
presentation of AD is characterized by loss of memory,  
20 cognition, reasoning, judgment, and orientation. As the disease  
progresses, motor, sensory, and linguistic abilities are also  
affected until there is global impairment of multiple cognitive  
functions. These cognitive losses occur gradually, but  
typically lead to severe impairment and eventual death in the  
25 range of four to twelve years.

Alzheimer's disease is characterized by two major  
pathologic observations in the brain: neurofibrillary tangles  
and beta amyloid (or neuritic) plaques, comprised predominantly  
of an aggregate of a peptide fragment know as A beta.  
30 Individuals with AD exhibit characteristic beta-amyloid deposits  
in the brain (beta amyloid plaques) and in cerebral blood  
vessels (beta amyloid angiopathy) as well as neurofibrillary  
tangles. Neurofibrillary tangles occur not only in Alzheimer's

disease but also in other dementia-inducing disorders. On autopsy, large numbers of these lesions are generally found in areas of the human brain important for memory and cognition.

5 Smaller numbers of these lesions in a more restricted anatomical distribution are found in the brains of most aged humans who do not have clinical AD. Amyloidogenic plaques and vascular amyloid angiopathy also characterize the brains of individuals with Trisomy 21 (Down's Syndrome), Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type (HCHWA-  
10 D), and other neurodegenerative disorders. Beta-amyloid is a defining feature of AD, now believed to be a causative precursor or factor in the development of disease. Deposition of A beta in areas of the brain responsible for cognitive activities is a major factor in the development of AD. Beta-amyloid plaques are  
15 predominantly composed of amyloid beta peptide (A beta, also sometimes designated betaA4). A beta peptide is derived by proteolysis of the amyloid precursor protein (APP) and is comprised of 39-42 amino acids. Several proteases called secretases are involved in the processing of APP.

20 Cleavage of APP at the N-terminus of the A beta peptide by beta-secretase and at the C-terminus by one or more gamma-secretases constitutes the beta-amyloidogenic pathway, i.e. the pathway by which A beta is formed. Cleavage of APP by alpha-secretase produces alpha-sAPP, a secreted form of APP that does  
25 not result in beta-amyloid plaque formation. This alternate pathway precludes the formation of A beta peptide. A description of the proteolytic processing fragments of APP is found, for example, in U.S. Patent Nos. 5,441,870; 5,721,130; and 5,942,400.

30 An aspartyl protease has been identified as the enzyme responsible for processing of APP at the beta-secretase cleavage site. The beta-secretase enzyme has been disclosed using varied nomenclature, including BACE, Asp, and Memapsin. See, for

example, Sindha et al., 1999, *Nature* 402:537-554 (p501) and published PCT application WO00/17369.

Several lines of evidence indicate that progressive cerebral deposition of beta-amyloid peptide (A beta) plays a seminal role in the pathogenesis of AD and can precede cognitive symptoms by years or decades. See, for example, Selkoe, 1991, *Neuron* 6:487. Release of A beta from neuronal cells grown in culture and the presence of A beta in cerebrospinal fluid (CSF) of both normal individuals and AD subjects has been demonstrated. See, for example, Seubert et al., 1992, *Nature* 359:325-327.

It has been proposed that A beta peptide accumulates as a result of APP processing by beta-secretase, thus inhibition of this enzyme's activity is desirable for the treatment of AD. In vivo processing of APP at the beta-secretase cleavage site is thought to be a rate-limiting step in A beta production, and is thus a therapeutic target for the treatment of AD. See for example, Sabbagh, M., et al., 1997, *Alz. Dis. Rev.* 3, 1-19.

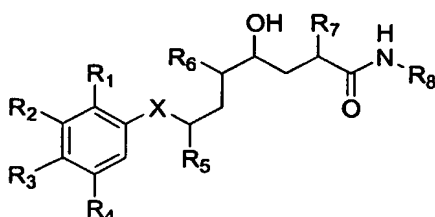
BACE1 knockout mice fail to produce A beta, and present a normal phenotype. When crossed with transgenic mice that over express APP, the progeny show reduced amounts of A beta in brain extracts as compared with control animals (Luo et al., 2001 *Nature Neuroscience* 4:231-232). This evidence further supports the proposal that inhibition of beta-secretase activity and reduction of A beta in the brain provides a therapeutic method for the treatment of AD and other beta amyloid disorders.

At present there are no effective treatments for halting, preventing, or reversing the progression of Alzheimer's disease. Therefore, there is an urgent need for pharmaceutical agents capable of slowing the progression of Alzheimer's disease and/or preventing it in the first place.

Compounds that are effective inhibitors of beta-secretase, that inhibit beta-secretase-mediated cleavage of APP, that are

effective inhibitors of A beta production, and/or are effective to reduce amyloid beta deposits or plaques, are needed for the treatment and prevention of disease characterized by amyloid beta deposits or plaques, such as AD.

- 5 U.S. Patent 5,559,111 discloses aryl-alkanoic acid amide compounds of the formula



formula 1

wherein

- 10  $R_1$  is hydrogen, hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy or free or esterified or amidated carboxy-lower alkoxy;
- $R_2$  is hydrogen, lower alkyl, cycloalkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, hydroxy, optionally lower alkanoylated, halogenated or sulfonylated hydroxy-lower alkoxy; amino-lower alkyl that is unsubstituted or substituted by lower alkyl, by lower alkanoyl and/or by lower alkoxy-carbonyl; optionally hydrogenated heteroaryl-lower alkyl; amino-lower
- 15 alkoxy that is substituted by lower alkyl, by lower alkanoyl and/or by lower alkoxy-carbonyl; oxo-lower alkoxy, lower alkoxy, cycloalkoxy, lower alkenyloxy, cycloalkoxy-lower alkoxy, lower alkoxy-lower alkoxy, lower alkoxy-lower alkenyl, lower alkenyloxy-lower alkoxy, lower alkoxy-lower alkenyloxy, lower alkenyloxy-lower alkyl, lower alkanoyl-lower alkoxy, optionally S-oxidised lower alkylthio-lower alkoxy, lower alkylthio-(hydroxy)-lower alkoxy, aryl-lower alkoxy, optionally hydrogenated heteroaryl-lower alkoxy, cyano-lower alkoxy, free or esterified or amidated carboxy-
- 20
- 25



lower alkoxy or free or esterified or amidated carboxy-lower alkyl;

5  $R_3$  is halogenated lower alkyl, lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, hydroxy-lower alkyl, optionally S-oxidised lower alkylthio-lower alkyl, optionally hydrogenated heteroarylthio-lower alkyl, optionally hydrogenated heteroaryl-lower alkyl; amino-lower alkyl that is unsubstituted or N-mono- or N,N-di-lower alkylated. N-lower alkanoylated or N-lower alkane-sulfonylated or N,N-disubstituted by lower alkylene, by unsubstituted or N'-lower alkylated or N'-lower alkanoylated aza-lower alkylene, by oxa-lower alkylene or by optionally S-oxidised thia-lower alkylene; cyano-lower alkyl, free or esterified or amidated carboxy-lower alkyl, cycloalkyl, aryl, hydroxy, 10 lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy, cycloalkoxy-lower alkoxy, hydroxy-lower alkoxy, aryl-lower alkoxy, optionally halogenated lower alkoxy, optionally S-oxidised lower alkylthio-lower alkoxy, optionally hydrogenated heteroaryl-lower alkoxy, optionally hydrogenated heteroarylthio-lower alkoxy; amino-lower alkoxy that is unsubstituted or N-mono- or N,N-di-lower alkylated. N-lower alkanoylated or N-lower alkanesulfonylated or substituted by lower alkylene, by unsubstituted or N'-lower alkylated or N'-lower alkanoylated aza-lower alkylene, by oxa-lower alkylene or by optionally S-oxidised thia-lower alkylene; cyano-lower alkoxy or free or esterified or amidated carboxy-lower alkoxy; 15

20  $R_4$  is hydrogen, lower alkyl, hydroxy, lower alkoxy or cycloalkoxy;

25 X is methylene;

$R_5$  is lower alkyl or cycloalkyl;

R<sub>6</sub> is unsubstituted or N-mono- or N,N-di-lower alkylated or N-lower alkanoylated amino;

R<sub>7</sub> is lower alkyl, lower alkenyl, cycloalkyl or aryl-lower alkyl; and

5 R<sub>8</sub> is lower alkyl, cycloalkyl, free or aliphatically esterified or etherified hydroxy-lower alkyl; amino-lower alkyl that is unsubstituted or N-lower alkanoylated or N-mono- or N,N-di-lower alkylated or N,N-disubstituted by lower alkylene, by hydroxy-lower alkoxy- or lower alkanoyloxy-lower alkylene, by  
10 unsubstituted or N'-lower alkanoylated or N'-lower alkylated aza-lower alkylene, by oxa-lower alkylene or by optionally S-oxidised thia-lower alkylene; free or esterified or amidated carboxy-lower alkyl, free or esterified or amidated dicarboxy-lower alkyl, free or esterified or amidated carboxy-(hydroxy)-  
15 lower alkyl, free or esterified or amidated carboxycycloalkyl-lower alkyl, cyano-lower alkyl, lower alkanesulfonyl-lower alkyl, unsubstituted or N-mono- or N,N-di-lower alkylated thiocarbamoyl-lower alkyl, unsubstituted or N-mono- or N,N-di-lower alkylated sulfamoyl-lower alkyl, or a heteroaryl radical  
20 bonded via a carbon atom and optionally hydrogenated and/or oxo-substituted, or lower alkyl substituted by a heteroaryl radical bonded via a carbon atom and optionally hydrogenated and/or oxo-substituted, or a pharmaceutically acceptable salt thereof.

U.S. Patent No. 5,559,111 discloses how to make the above  
25 compounds and how to use them as renin inhibiting compounds in the treatment of disorders related to hypertension. The disclosure of U.S. Patent No. 5,559,111 is incorporated herein by reference in its entirety.

SUMMARY OF INVENTION

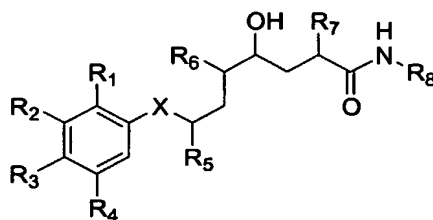
The present invention relates to methods of treating a subject who has, or in preventing a subject from developing, a disease or condition selected from the group consisting of

5 Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for helping to slow the progression of Alzheimer's disease, for treating subjects with mild cognitive impairment (MCI) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD,

10 for treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative dementias,

15 including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, or diffuse Lewy body type of Alzheimer's disease and who is in need of such

20 treatment which comprises administration of a therapeutically effective amount of a compound of formula 1:



formula 1

wherein

- 25 R<sub>1</sub> is hydrogen, hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy or free or esterified or amidated carboxy-lower alkoxy;
- R<sub>2</sub> is hydrogen, lower alkyl, cycloalkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkoxy-lower alkyl, cycloalkoxy-

lower alkyl, hydroxy, optionally lower alkanoylated, halogenated or sulfonylated hydroxy-lower alkoxy; amino-lower alkyl that is unsubstituted or substituted by lower alkyl, by lower alkanoyl and/or by lower alkoxycarbonyl; optionally hydrogenated heteroaryl-lower alkyl; amino-lower alkoxy that is substituted by lower alkyl, by lower alkanoyl and/or by lower alkoxycarbonyl; oxo-lower alkoxy, lower alkoxy, cycloalkoxy, lower alkenyloxy, cycloalkoxy-lower alkoxy, lower alkoxy-lower alkoxy, lower alkoxy-lower alkenyl, lower alkenyloxy-lower alkoxy, lower alkoxy-lower alkenyloxy, lower alkenyloxy-lower alkyl, lower alkanoyl-lower alkoxy, optionally S-oxidised lower alkylthio-lower alkoxy, lower alkylthio-(hydroxy)-lower alkoxy, aryl-lower alkoxy, optionally hydrogenated heteroaryl-lower alkoxy, cyano-lower alkoxy, free or esterified or amidated carboxy-lower alkoxy or free or esterified or amidated carboxy-lower alkyl;

R<sub>3</sub> is halogenated lower alkyl, lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, hydroxy-lower alkyl, optionally S-oxidised lower alkylthio-lower alkyl, optionally hydrogenated heteroarylthio-lower alkyl, optionally hydrogenated heteroaryl-lower alkyl; amino-lower alkyl that is unsubstituted or N-mono- or N,N-di-lower alkylated. N-lower alkanoylated or N-lower alkane-sulfonylated or N,N-disubstituted by lower alkylene, by unsubstituted or N'-lower alkylated or N'-lower alkanoylated aza-lower alkylene, by oxa-lower alkylene or by optionally S-oxidised thia-lower alkylene; cyano-lower alkyl, free or esterified or amidated carboxy-lower alkyl, cycloalkyl, aryl, hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy, cycloalkoxy-lower alkoxy, hydroxy-lower alkoxy, aryl-lower alkoxy, optionally halogenated lower alkoxy, optionally S-oxidised lower alkylthio-lower alkoxy, optionally

hydrogenated heteroaryl-lower alkoxy, optionally  
hydrogenated heteroarylthio-lower alkoxy; amino-lower  
alkoxy that is unsubstituted or N-mono- or N,N-di-lower  
alkylated. N-lower alkanoylated or N-lower  
5 alkanesulfonylated or substituted by lower alkylene, by  
unsubstituted or N'-lower alkylated or N'-lower  
alkanoylated aza-lower alkylene, by oxa-lower alkylene or  
by optionally S-oxidised thia-lower alkylene; cyano-lower  
alkoxy or free or esterified or amidated carboxy-lower  
10 alkoxy;

R<sub>4</sub> is hydrogen, lower alkyl, hydroxy, lower alkoxy or  
cycloalkoxy;

X is methylene;

R<sub>5</sub> is lower alkyl or cycloalkyl;

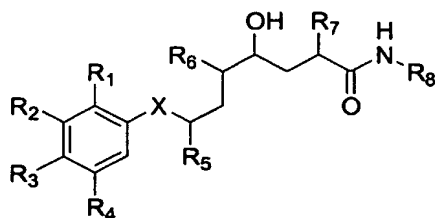
15 R<sub>6</sub> is unsubstituted or N-mono- or N,N-di-lower alkylated or N-  
lower alkanoylated amino;

R<sub>7</sub> is lower alkyl, lower alkenyl, cycloalkyl or aryl-lower  
alkyl; and

R<sub>8</sub> is lower alkyl, cycloalkyl, free or aliphatically esterified  
20 or etherified hydroxy-lower alkyl; amino-lower alkyl that  
is unsubstituted or N-lower alkanoylated or N-mono- or N,N-  
di-lower alkylated or N,N-disubstituted by lower alkylene,  
by hydroxy-, lower alkoxy- or lower alkanoyloxy-lower  
alkylene, by unsubstituted or N'-lower alkanoylated or N'-  
25 lower alkylated aza-lower alkylene, by oxa-lower alkylene  
or by optionally S-oxidised thia-lower alkylene; free or  
esterified or amidated carboxy-lower alkyl, free or  
esterified or amidated dicarboxy-lower alkyl, free or  
esterified or amidated carboxy-(hydroxy)-lower alkyl, free  
30 or esterified or amidated carboxycycloalkyl-lower alkyl,  
cyano-lower alkyl, lower alkanesulfonyl-lower alkyl,  
unsubstituted or N-mono- or N,N-di-lower alkylated  
thiocarbamoyl-lower alkyl, unsubstituted or N-mono- or N,N-

di-lower alkylated sulfamoyl-lower alkyl, or a heteroaryl radical bonded via a carbon atom and optionally hydrogenated and/or oxo-substituted, or lower alkyl substituted by a heteroaryl radical bonded via a carbon atom and optionally hydrogenated and/or oxo-substituted, or a pharmaceutically acceptable salt thereof.

The invention also provides intermediates and methods useful for preparing the compounds of formula 1



formula 1

wherein

R<sub>1</sub> is hydrogen, hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy or free or esterified or amidated carboxy-lower alkoxy;

R<sub>2</sub> is hydrogen, lower alkyl, cycloalkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, hydroxy, optionally lower alkanoylated, halogenated or sulfonylated hydroxy-lower alkoxy; amino-lower alkyl that is unsubstituted or substituted by lower alkyl, by lower alkanoyl and/or by lower alkoxycarbonyl; optionally hydrogenated heteroaryl-lower alkyl; amino-lower alkoxy that is substituted by lower alkyl, by lower alkanoyl and/or by lower alkoxycarbonyl; oxo-lower alkoxy, lower alkoxy, cycloalkoxy, lower alkenyloxy, cycloalkoxy-lower alkoxy, lower alkoxy-lower alkoxy, lower alkoxy-lower alkenyl, lower alkenyloxy-lower alkoxy, lower alkoxy-lower alkenyloxy, lower alkenyloxy-lower alkyl, lower alkanoyl-lower alkoxy, optionally S-oxidised lower alkylthio-lower

alkoxy, lower alkylthio-(hydroxy)-lower alkoxy, aryl-lower alkoxy, optionally hydrogenated heteroaryl-lower alkoxy, cyano-lower alkoxy, free or esterified or amidated carboxy-lower alkoxy or free or esterified or amidated carboxy-lower alkyl;

5  $R_3$  is halogenated lower alkyl, lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, hydroxy-lower alkyl, optionally S-oxidised lower alkylthio-lower alkyl, optionally hydrogenated heteroarylthio-lower alkyl, optionally hydrogenated heteroaryl-lower alkyl; amino-lower alkyl that is unsubstituted or N-mono- or N,N-di-lower alkylated. N-lower alkanoylated or N-lower alkane-sulfonylated or N,N-disubstituted by lower alkylene, by unsubstituted or N'-lower alkylated or N'-lower alkanoylated aza-lower alkylene, by oxa-lower alkylene or by optionally S-oxidised thia-lower alkylene; cyano-lower alkyl, free or esterified or amidated carboxy-lower alkyl, cycloalkyl, aryl, hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy, cycloalkoxy-lower alkoxy, hydroxy-lower alkoxy, aryl-lower alkoxy, optionally halogenated lower alkoxy, optionally S-oxidised lower alkylthio-lower alkoxy, optionally hydrogenated heteroaryl-lower alkoxy, optionally hydrogenated heteroarylthio-lower alkoxy; amino-lower alkoxy that is unsubstituted or N-mono- or N,N-di-lower alkylated. N-lower alkanoylated or N-lower alkanesulfonylated or substituted by lower alkylene, by unsubstituted or N'-lower alkylated or N'-lower alkanoylated aza-lower alkylene, by oxa-lower alkylene or by optionally S-oxidised thia-lower alkylene; cyano-lower alkoxy or free or esterified or amidated carboxy-lower alkoxy;

30  $R_4$  is hydrogen, lower alkyl, hydroxy, lower alkoxy or cycloalkoxy;

X is methylene;

R<sub>5</sub> is lower alkyl or cycloalkyl;

R<sub>6</sub> is unsubstituted or N-mono- or N,N-di-lower alkylated or N-lower alkanoylated amino;

5 R<sub>7</sub> is lower alkyl, lower alkenyl, cycloalkyl or aryl-lower alkyl; and

R<sub>8</sub> is lower alkyl, cycloalkyl, free or aliphatically esterified or etherified hydroxy-lower alkyl; amino-lower alkyl that is unsubstituted or N-lower alkanoylated or N-mono- or N,N-di-lower alkylated or N,N-disubstituted by lower alkylene, by hydroxy-, lower alkoxy- or lower alkanoyloxy-lower alkylene, by unsubstituted or N'-lower alkanoylated or N'-lower alkylated aza-lower alkylene, by oxa-lower alkylene or by optionally S-oxidised thia-lower alkylene; free or  
10 esterified or amidated carboxy-lower alkyl, free or esterified or amidated dicarboxy-lower alkyl, free or esterified or amidated carboxy-(hydroxy)-lower alkyl, free or esterified or amidated carboxycycloalkyl-lower alkyl, cyano-lower alkyl, lower alkanesulfonyl-lower alkyl,  
15 unsubstituted or N-mono- or N,N-di-lower alkylated thiocarbamoyl-lower alkyl, unsubstituted or N-mono- or N,N-di-lower alkylated sulfamoyl-lower alkyl, or a heteroaryl radical bonded via a carbon atom and optionally hydrogenated and/or oxo-substituted, or lower alkyl  
20 substituted by a heteroaryl radical bonded via a carbon atom and optionally hydrogenated and/or oxo-substituted, or  
25 a pharmaceutically acceptable salt thereof. .

The invention also provides use of a compound of formula 1,  
30 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament.



The invention also provides methods for inhibiting beta-secretase activity, for inhibiting cleavage of amyloid precursor protein (APP), in a reaction mixture, at a site between Met596 and Asp597, numbered for the APP-695 amino acid isotype, or at a corresponding site of an isotype or mutant thereof; for inhibiting production of amyloid beta peptide (A beta) in a cell; for inhibiting the production of beta-amyloid plaque in an animal; and for treating or preventing a disease characterized by beta-amyloid deposits in the brain. These methods each include administration of a therapeutically effective amount of a compound of formula 1, or a pharmaceutically acceptable salt thereof.

The present invention also includes a method for inhibiting beta-secretase activity, including exposing said beta-secretase to an effective inhibitory amount of a compound of formula 1, or a pharmaceutically acceptable salt thereof.

The present invention also includes a method for inhibiting cleavage of amyloid precursor protein (APP), in a reaction mixture, at a site between Met596 and Asp597, numbered for the APP-695 amino acid isotype; or at a corresponding site of an isotype or mutant thereof, including exposing said reaction mixture to an effective inhibitory amount of a compound of formula 1, or a pharmaceutically acceptable salt thereof.

The present invention also includes a method for inhibiting the production of beta-amyloid plaque in an animal, including administering to said animal an effective inhibitory amount of a compound of formula 1, or a pharmaceutically acceptable salt thereof.

The present invention also includes a method for treating or preventing a disease characterized by beta-amyloid deposits in the brain including administering to a subject an effective

therapeutic amount of a compound of formula 1, or a pharmaceutically acceptable salt thereof.

The present invention also includes a composition including beta-secretase complexed with a compound of formula 1, or a pharmaceutically acceptable salt thereof.

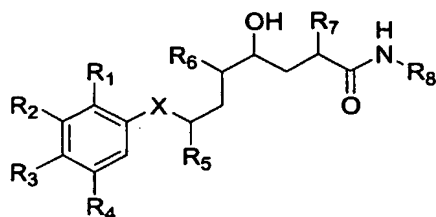
The present invention also includes a component kit including component parts capable of being assembled, in which at least one component part includes a compound of formula 1 enclosed in a container.

The present invention also includes a container kit including a plurality of containers, each container including one or more unit dose of a compound of formula 1, or a pharmaceutically acceptable salt thereof.

#### DETAILED DESCRIPTION OF THE INVENTION

In one aspect, the present invention relates to methods of treating a subject who has, or in preventing a subject from developing, a disease or condition selected from the group consisting of Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for helping to slow the progression of Alzheimer's disease, for treating subjects with mild cognitive impairment (MCI) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, or diffuse Lewy

body type of Alzheimer's disease and who is in need of such treatment which comprises administration of a therapeutically effective amount of a compound of formula 1:



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where  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$ ,  $R_8$ , and  $X$  are as defined above.

In one aspect, this method of treatment can be used where the disease is Alzheimer's disease.

In another aspect, this method of treatment can help prevent or delay the onset of Alzheimer's disease.

In another aspect, this method of treatment can help slow the progression of Alzheimer's disease.

In another aspect, this method of treatment can be used where the disease is mild cognitive impairment.

In another aspect, this method of treatment can be used where the disease is Down's syndrome.

In another aspect, this method of treatment can be used where the disease is Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type.

In another aspect, this method of treatment can be used where the disease is cerebral amyloid angiopathy.

In another aspect, this method of treatment can be used where the disease is degenerative dementias.

In another aspect, this method of treatment can be used where the disease is diffuse Lewy body type of Alzheimer's disease.

In another aspect, this method of treatment can treat an existing disease, such as those listed above.

In another aspect, this method of treatment can prevent a disease, such as those listed above, from developing or progressing.

In another aspect, the invention provides a method of treating a subject who has, or in preventing a subject from getting, a disease or condition selected from the group consisting of Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for treating subjects with mild cognitive impairment (MCI) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, or diffuse Lewy body type of Alzheimer's disease and who is in need of such treatment which includes administration of a therapeutically effective amount of a compound of formula (I-A), or a pharmaceutically acceptable salt thereof.

The present invention also includes the use of a compound of formula 1, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for use in treating a subject who has, or in preventing a subject from developing, a disease or condition selected from the group consisting of Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for treating subjects with mild cognitive impairment (MCI) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating

Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobar  
5 hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body  
10 type of Alzheimer's disease and who is in need of such treatment.

In one aspect, this use of a compound of formula 1 can be employed where the disease is Alzheimer's disease.

In another aspect, this use of a compound of formula 1 can  
15 help prevent or delay the onset of Alzheimer's disease.

In another aspect, this use of a compound of formula 1 can help slow the progression of Alzheimer's disease.

In another aspect, this use of a compound of formula 1 can be employed where the disease is mild cognitive impairment.

20 In another aspect, this use of a compound of formula 1 can be employed where the disease is Down's syndrome.

In another aspect, this use of a compound of formula 1 can be employed where the disease is Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type.

25 In another aspect, this use of a compound of formula 1 can be employed where the disease is cerebral amyloid angiopathy.

In another aspect, this use of a compound of formula 1 can be employed where the disease is degenerative dementias.

In another aspect, this use of a compound of formula 1 can  
30 be employed where the disease is diffuse Lewy body type of Alzheimer's disease.

In a preferred aspect, this use of a compound of formula 1 is a pharmaceutically acceptable salt of an acid selected from

the group consisting of acids hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, citric, methanesulfonic,  $\text{CH}_3-(\text{CH}_2)_n-\text{COOH}$  where  $n$  is 0 thru 4,  $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$  where  $n$  is as defined above,  $\text{HOOC}-\text{CH}=\text{CH}-\text{COOH}$ , and  
5 phenyl-COOH.

The present invention also includes methods for inhibiting beta-secretase activity, for inhibiting cleavage of amyloid precursor protein (APP), in a reaction mixture, at a site between Met596 and Asp597, numbered for the APP-695 amino acid  
10 isotype, or at a corresponding site of an isotype or mutant thereof; for inhibiting production of amyloid beta peptide (A beta) in a cell; for inhibiting the production of beta-amyloid plaque in an animal; and for treating or preventing a disease characterized by beta-amyloid deposits in the brain. These  
15 methods each include administration of a therapeutically effective amount of a compound of formula 1, or a pharmaceutically acceptable salt thereof.

The present invention also includes a method for inhibiting beta-secretase activity, including exposing said beta-secretase  
20 to an effective inhibitory amount of a compound of formula 1, or a pharmaceutically acceptable salt thereof.

In one aspect, this method includes exposing said beta-secretase to said compound *in vitro*.

In another aspect, this method includes exposing said beta-secretase to said compound in a cell.  
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In another aspect, this method includes exposing said beta-secretase to said compound in a cell in an animal.

In another aspect, this method includes exposing said beta-secretase to said compound in a human.  
30

The present invention also includes a method for inhibiting cleavage of amyloid precursor protein (APP), in a reaction mixture, at a site between Met596 and Asp597, numbered for the

APP-695 amino acid isotype; or at a corresponding site of an isotype or mutant thereof, including exposing said reaction mixture to an effective inhibitory amount of a compound of formula 1, or a pharmaceutically acceptable salt thereof.

5        In one aspect, this method employs a cleavage site: between Met652 and Asp653, numbered for the APP-751 isotype; between Met 671 and Asp 672, numbered for the APP-770 isotype; between Leu596 and Asp597 of the APP-695 Swedish Mutation; between Leu652 and Asp653 of the APP-751 Swedish Mutation; or  
10 between Leu671 and Asp672 of the APP-770 Swedish Mutation.

      In another aspect, this method exposes said reaction mixture *in vitro*.

      In another aspect, this method exposes said reaction mixture in a cell.

15        In another aspect, this method exposes said reaction mixture in an animal cell.

      In another aspect, this method exposes said reaction mixture in a human cell.

20        The present invention also includes a method for inhibiting production of amyloid beta peptide (A beta) in a cell, including administering to said cell an effective inhibitory amount of a compound of formula 1, or a pharmaceutically acceptable salt thereof.

25        In an embodiment, this method includes administering to an animal.

      In an embodiment, this method includes administering to a human.

30        The present invention also includes a method for inhibiting the production of beta-amyloid plaque in an animal, including administering to said animal an effective inhibitory amount of a compound of formula 1, or a pharmaceutically acceptable salt thereof.

In one embodiment of this aspect, this method includes administering to a human.

The present invention also includes a method for treating or preventing a disease characterized by beta-amyloid deposits  
5 in the brain including administering to a subject an effective therapeutic amount of a compound of formula 1, or a pharmaceutically acceptable salt thereof.

In one aspect, this method employs a compound at a therapeutic amount in the range of from about 0.1 to about 1000  
10 mg/day.

In another aspect, this method employs a compound at a therapeutic amount in the range of from about 15 to about 1500 mg/day.

In another aspect, this method employs a compound at a  
15 therapeutic amount in the range of from about 1 to about 100 mg/day.

In another aspect, this method employs a compound at a therapeutic amount in the range of from about 5 to about 50 mg/day.

20 In another aspect, this method can be used where said disease is Alzheimer's disease.

In another aspect, this method can be used where said disease is Mild Cognitive Impairment, Down's Syndrome, or Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch  
25 Type.

The present invention also includes a composition including beta-secretase complexed with a compound of formula 1, or a pharmaceutically acceptable salt thereof.

The present invention also includes a method for producing  
30 a beta-secretase complex including exposing beta-secretase to a compound of formula 1, or a pharmaceutically acceptable salt thereof, in a reaction mixture under conditions suitable for the production of said complex.



In an embodiment, this method employs exposing *in vitro*.

In an embodiment, this method employs a reaction mixture that is a cell.

The present invention also includes a component kit  
5 including component parts capable of being assembled, in which  
at least one component part includes a compound of formula 1  
enclosed in a container.

In an embodiment, this component kit includes lyophilized  
compound, and at least one further component part includes a  
10 diluent.

The present invention also includes a container kit  
including a plurality of containers, each container including  
one or more unit dose of a compound of formula 1, or a  
pharmaceutically acceptable salt thereof.

15 In an embodiment, this container kit includes each  
container adapted for oral delivery and includes a tablet, gel,  
or capsule.

In an embodiment, this container kit includes each  
container adapted for parenteral delivery and includes a depot  
20 product, syringe, ampoule, or vial.

In an embodiment, this container kit includes each  
container adapted for topical delivery and includes a patch,  
medipad, ointment, or cream.

25 The present invention also includes an agent kit including  
a compound of formula 1, or a pharmaceutically acceptable salt  
thereof; and one or more therapeutic agents selected from the  
group consisting of an antioxidant, an anti-inflammatory, a  
gamma secretase inhibitor, a neurotrophic agent, an acetyl  
30 cholinesterase inhibitor, a statin, an A beta peptide, and an  
anti-A beta antibody.

The present invention provides compounds, compositions,  
kits, and methods for inhibiting beta-secretase-mediated

cleavage of amyloid precursor protein (APP). More particularly, the compounds, compositions, and methods of the invention are effective to inhibit the production of A beta peptide and to treat or prevent any human or veterinary disease or condition associated with a pathological form of A beta peptide.

The invention provides methods, as described above, of using compounds of formula 1 wherein

R<sub>1</sub> is hydrogen, hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy, carboxy-lower alkoxy, lower alkoxycarbonyl-lower alkoxy, carbamoyl-lower alkoxy or N-mono- or N,N-di-lower alkylcarbamoyl-lower alkoxy,

R<sub>2</sub> is hydrogen, lower alkyl, cycloalkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, hydroxy, lower alkanoyloxy-lower alkyl, hydroxy-lower alkoxy, halo-(hydroxy)-lower alkoxy, lower alkanesulfonyl-(hydroxy)-lower alkoxy, amino-lower alkyl, lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, lower alkanoylamino-lower alkyl, lower alkoxycarbonyl-amino-lower alkyl, amino-lower alkoxy, lower alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy, lower alkanoylamino-lower alkoxy, lower alkoxycarbonyl-amino-lower alkoxy, oxo-lower alkoxy, lower alkoxy, cycloalkoxy, lower alkenyloxy, cycloalkoxy-lower alkoxy, lower alkoxy-lower alkoxy, lower alkoxy-lower alkenyl, lower alkenyloxy-lower alkoxy, lower alkoxy-lower alkenyloxy, lower alkenyloxy-lower alkyl, lower alkanoyl-lower alkoxy, lower alkylthio-lower alkoxy, lower alkanesulfonyl-lower alkoxy, lower alkylthio-(hydroxy)-lower alkoxy, aryl-lower alkoxy, thiazolylthio-lower alkoxy or thiazolinylthio-lower alkoxy, imidazolylthio-lower alkoxy, optionally N-oxidised pyridylthio-lower alkoxy, pyrimidinylthio-lower alkoxy, cyano-lower alkoxy, lower

alkoxycarbonyl-lower alkoxy, carbamoyl-lower alkoxy, N-mono- or N,N-di-lower alkylcarbamoyl-lower alkoxy, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, carbamoyl-lower alkyl or N-mono- or N,N-di-lower alkylcarbamoyl-lower alkyl;

R<sub>3</sub> is lower alkyl, polyhalo-lower alkyl, lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, hydroxy-lower alkyl, lower alkylthio-lower alkyl, lower alkanesulfonyl-lower alkyl, optionally partially hydrogenated or N-oxidised pyridyl-lower alkyl, thiazolyl-thio-lower alkyl or thiazolinythio-lower alkyl, imidazolylthio-lower alkyl, optionally N-oxidised pyridylthio-lower alkyl, pyrimidinylthio-lower alkyl, amino-lower alkyl, lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, lower alkanoyl-amino-lower alkyl, lower alkanesulfonylamino-lower alkyl, polyhalo-lower alkane-sulfonylamino-lower alkyl, pyrrolidino-lower alkyl, piperidino-lower alkyl, piperazino-, N'-lower alkylpiperazino- or N'-lower alkanoylpiperazino-lower alkyl, morpholino-lower alkyl, thiomorpholino-, S-oxothiomorpholino- or S,S-dioxothio-morpholino-lower alkyl, cyano-lower alkyl, carboxy-lower alkyl, lower alkoxy-carbonyl-lower alkyl, carbamoyl-lower alkyl, N-mono- or N,N-di-lower alkyl-carbamoyl-lower alkyl, cycloalkyl; phenyl or naphthyl that is unsubstituted or mono-, di- or tri-substituted by lower alkyl, lower alkoxy, hydroxy, lower alkylamino, di-lower alkylamino, halogen and/or by trifluoromethyl; hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy, cycloalkoxy-lower alkoxy, hydroxy-lower alkoxy; phenyl-lower alkoxy or naphthyl-lower alkoxy that is unsubstituted or mono-, di- or tri-substituted by lower alkyl, lower alkoxy, hydroxy, lower alkylamino, di-lower alkylamino, halogen and/or by trifluoromethyl; lower alkoxy, polyhalo-lower alkoxy, lower alkylthio-lower

alkoxy, lower alkanesulfonyl-lower alkoxy, optionally hydrogenated heteroaryl-lower alkoxy, optionally partially or fully hydrogenated heteroarylthio-lower alkoxy, such as thiazolylthio-lower alkoxy or thiazolinythio-lower alkoxy, imidazolylthio-lower alkoxy, optionally N-oxidised pyridylthio-lower alkoxy, pyrimidinylthio-lower alkoxy, amino-lower alkoxy, lower alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy, lower alkanoylamino-lower alkoxy, lower alkanesulfonylamino-lower alkoxy, polyhalo-lower alkanesulfonylamino-lower alkoxy, pyrrolidino-lower alkoxy, piperidino-lower alkoxy, piperazino-, N'-lower alkylpiperazino- or N'-lower alkanoylpiperazino-lower alkoxy, morpholino-lower alkoxy, thiomorpholino-, S-oxothiomorpholino- or S,S-dioxothiomorpholino-lower alkoxy, cyano-lower alkoxy, carboxy-lower alkoxy, lower alkoxy carbonyl-lower alkoxy, carbamoyl-lower alkoxy or N-mono- or N,N-di-lower alkylcarbamoyl-lower alkoxy; or together with R<sub>4</sub> is lower alkylenedioxy or a fused-on benzo or cyclohexeno ring;

R<sub>4</sub> together with R<sub>3</sub> is lower alkylenedioxy or a fused-on benzo or cyclohexeno ring, or is hydrogen, lower alkyl, hydroxy, lower alkoxy or cycloalkoxy;

X is methylene or hydroxymethylene;

R<sub>5</sub> is lower alkyl or cycloalkyl;

R<sub>6</sub> is amino, lower alkylamino; di-lower alkylamino or lower alkanoylamino;

R<sub>7</sub> is lower alkyl, lower alkenyl, cycloalkyl, or phenyl- or naphthyl-lower alkyl that is unsubstituted or mono-, di- or tri-substituted by lower alkyl, lower alkoxy, hydroxy, lower alkylamino, di-lower alkylamino, halogen and/or by trifluoromethyl; and

R<sub>8</sub> is lower alkyl, cycloalkyl, hydroxy-lower alkyl, lower alkanoyloxy-lower alkyl, lower alkoxy-lower alkyl or lower

alkenyloxy-lower alkyl, amino-lower alkyl, lower  
alkanoylamino-lower alkyl, N-mono- or N,N-di-lower  
alkylamino-lower alkyl, optionally hydroxylated or lower  
alkoxylated piperidino-lower alkyl, such as piperidino-  
5 lower alkyl, hydroxypiperidino-lower alkyl or lower  
alkoxypiperidino-lower alkyl, piperazino-, N'-lower  
alkylpiperazino- or N'-lower alkanoylpiperazino-lower  
alkyl, unsubstituted or lower alkylated morpholino-lower  
alkyl, such as morpholino-lower alkyl or  
10 dimethylmorpholino-lower alkyl, or optionally S-oxidised  
thiomorpholino-lower alkyl, such as thiomorpholino-lower  
alkyl, S,S-dioxothiomorpholino-lower alkyl, carboxy-lower  
alkyl, lower alkoxycarbonyl-lower alkyl, carbamoyl-lower  
alkyl, N-mono- or N,N-di-lower alkylcarbamoyl-lower alkyl,  
15 dicarboxy-lower alkyl, di-lower alkoxycarbonyl-lower alkyl,  
dicarbamoyl-lower alkyl, di-(N-mono- or N,N-di-lower  
alkylcarbamoyl)-lower alkyl, carboxy-(hydroxy)-lower alkyl,  
lower alkoxy-carbonyl-(hydroxy)-lower alkyl or carbamoyl-  
(hydroxy)-lower alkyl, cyano-lower alkyl, lower  
20 alkanesulfonyl-lower alkyl, sulfamoyl-lower alkyl, lower  
alkyl-sulfamoyl-lower alkyl, di-lower alkylsulfamoyl-lower  
alkyl, thiocarbamoyl-lower alkyl, lower alkylthiocarbamoyl-  
lower alkyl, di-lower alkylthiocarbamoyl-lower alkyl,  
pyrrolidinyl, imidazolyl, benzimidazolyl, oxadiazolyl,  
25 pyridyl, oxopiperidinyl, quinolinyl, unsubstituted or N-  
lower alkanoylated piperidyl or pyrrolidinyl, imidazolyl-  
lower alkyl, benzimidazolyl-lower alkyl, oxadiazolyl-lower  
alkyl, pyridyl-lower alkyl, unsubstituted or N-lower  
alkanoylated piperidyl-lower alkyl or pyrrolidinyl-lower  
30 alkyl, oxopiperidinyl-lower alkyl, quinolinyl-lower alkyl,  
morpholino-carbonyl-lower alkyl or unsubstituted or N-lower  
alkanoylated piperidyl-lower alkyl, and the  
pharmaceutically acceptable salts thereof.

The invention provides methods, as described above, of using compounds of formula 1 wherein

R<sub>1</sub> is hydrogen;

5 R<sub>2</sub> is lower alkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkoxy, lower alkoxy-lower alkoxy-lower alkyl; phenyl-lower alkoxy that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen, nitro and/or by amino; optionally N-oxidised pyridyl-lower alkoxy, lower  
10 alkylthio-lower alkoxy, lower alkane-sulfonyl-lower alkoxy, lower alkanoyl-lower alkoxy, optionally N-oxidised pyridyl-lower alkoxy, cyano-lower alkoxy, carboxy-lower alkoxy, lower alkoxycarbonyl-lower alkoxy, carbamoyl-lower alkoxy, lower alkylcarbamoyl-lower alkoxy or di-lower  
15 alkylcarbamoyl-lower alkoxy;

R<sub>3</sub> is hydrogen, lower alkyl, hydroxy, lower alkoxy or polyhalo-lower alkoxy; or

R<sub>3</sub> together with R<sub>4</sub> is lower alkylenedioxy;

R<sub>4</sub> is hydrogen or together with R<sub>3</sub> is lower alkylidenedioxy;

20 X is methylene or hydroxymethylene;

R<sub>5</sub> is lower alkyl or cycloalkyl;

R<sub>6</sub> is amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino;

R<sub>7</sub> is lower alkyl; and

25 R<sub>8</sub> is lower alkyl, hydroxy, lower alkyl, lower alkanoyl-lower alkyl, lower alkoxy-lower alkyl, lower alkenyloxy-lower alkyl, amino-lower alkyl, lower alkanoylamino-lower alkyl, such as 2-(C<sub>1</sub>-C<sub>4</sub> alkanoylamino)-2-methyl-propyl, such as 2-acetylamino-2-methyl-propyl or 2-formylamino-2-methyl-propyl, N-mono- or N,N-di-lower alkylamino-lower alkyl,  
30 piperidino-lower alkyl, hydroxypiperidino-lower alkyl, lower alkoxypiperidino-lower alkyl, morpholino-lower alkyl, dimethylmorpholino-lower alkyl, thiomorpholino-lower alkyl,

S,S-dioxothiomorpholino-lower alkyl, carboxy-lower alkyl, lower alkoxy-carbonyl-lower alkyl, carbamoyl-lower alkyl, N-mono- or N,N-di-lower alkylcarbamoyl-lower alkyl, carboxy-(hydroxy)-lower alkyl, lower alkoxy-carbonyl-(hydroxy)-lower alkyl, carbamoyl-(hydroxy)-lower alkyl, 5- or 6-membered carboxycycloalkyl-lower alkyl, 5- or 6-membered lower alkoxy-carbonyl-cycloalkyl-lower alkyl, 5- or 6-membered carbamoylcycloalkyl-lower alkyl, 5- or 6-membered N-mono- or N,N-di-lower alkylcarbamoylcycloalkyl-lower alkyl, cyano-lower alkyl, lower alkanesulfonyl-lower alkyl, sulfamoyl-lower alkyl, lower alkylsulfamoyl-lower alkyl, or di-lower alkylsulfamoyl-lower alkyl, imidazolyl-lower alkyl, oxopyrrolidinyl-lower alkyl, benzimidazolyl-lower alkyl, oxadiazolyl-lower alkyl, pyridyl-lower alkyl, oxopiperidinyl-lower alkyl or quinolinyl-lower alkyl, piperidin-4-yl-lower alkyl or 1-C<sub>1</sub> -C<sub>7</sub> -lower alkanoylpiperidin-4-yl-lower alkyl, and the salts thereof.

The invention provides methods, as described above, of using compounds of formula 1 wherein

R<sub>1</sub> and R<sub>4</sub> are hydrogen;

R<sub>2</sub> is C<sub>1</sub> -C<sub>4</sub> alkoxy-C<sub>1</sub> -C<sub>4</sub> alkoxy, such as 3-methoxypropyloxy, or C<sub>1</sub> -C<sub>4</sub> alkoxy-C<sub>1</sub> -C<sub>4</sub> alkyl, such as 4-methoxybutyl;

R<sub>3</sub> is C<sub>1</sub> -C<sub>4</sub> alkyl, such as isopropyl or tert-butyl, or C<sub>1</sub> -C<sub>4</sub> alkoxy, such as methoxy;

R<sub>6</sub> is amino;

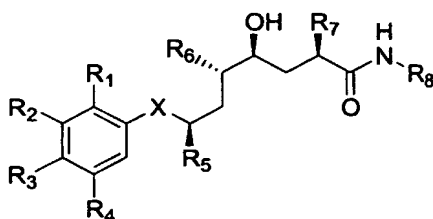
X is methylene;

R<sub>5</sub> and R<sub>7</sub> are branched C<sub>1</sub> -C<sub>4</sub> alkyl, such as isopropyl; and

R<sub>8</sub> is carbamoyl-C<sub>1</sub> -C<sub>4</sub> alkyl, such as 2- or 3-carbamoylpropyl, 2-(3-carbamoyl)propyl or 1-(2-carbamoyl-2-methyl)propyl, N-C<sub>1</sub> -C<sub>4</sub> alkylcarbamoyl-C<sub>1</sub> -C<sub>4</sub> alkyl, such as 3-(N-methylcarbamoyl)propyl, 1-(N-methylcarbamoyl)prop-2-yl, 2-(N-methyl-carbamoyl)prop-1-yl, especially 2(R)-(N-

methylcarbamoyl)prop-1-yl, N,N-di-C<sub>1</sub> -C<sub>4</sub> alkylcarbamoyl-C<sub>1</sub> -  
 C<sub>4</sub> alkyl, such as N,N-dimethylcarbamoylmethyl or 2-(N,N-  
 dimethylcarbamoyl)ethyl, 3-(N,N-dimethylcarbamoyl)propyl,  
 morpholino-C<sub>1</sub> -C<sub>4</sub> alkyl, such as 2-morpholinoethyl, 3-  
 5 morpholinopropyl or 1-(2-morpholino-2-methyl)propyl,  
 thiomorpholino-C<sub>1</sub> -C<sub>4</sub> alkyl, such as 2-thiomorpholinoethyl,  
 4-(1-C<sub>1</sub> -C<sub>4</sub> alkanoylpiperidyl)-C<sub>1</sub> -C<sub>4</sub> alkyl, such as 2-[4-  
 (1-acetyl)piperidinyl]ethyl, 2-oxopyrrolidinyl-C<sub>1</sub> -C<sub>4</sub>  
 10 alkyl, such as 2-oxopyrrolidin-5(S)-ylmethyl or 2-  
 oxopyrrolidin-5(R)-ylmethyl, and the salts thereof.

Preferred methods, as described above, use those compounds  
 of formula 1 wherein at least one, for example one, two, or  
 preferably all four, of the asymmetric carbon atoms of the main  
 15 chain have the stereochemical configuration shown in formula 1a



formula 1a

the variables each being as defined above, and the  
 pharmaceutically acceptable salts thereof.

20 Accordingly, the invention relates preferably to methods,  
 as described above, of using compounds of formula 1 wherein at  
 least one, for example one, two, or preferably all four, of the  
 asymmetric carbon atoms of the main chain have the  
 stereochemical configuration shown in formula 1a.

25 The invention relates to those methods, as described above,  
 wherein in the compounds of formulae I and Ia X is methylene.

The invention relates to the methods of using the compounds  
 of formula 1 as described in the Examples (herein below) and to



the salts thereof, especially the pharmaceutically acceptable salts thereof.

The invention relates to methods, as described above, of using aryl-alkanoic acid amides of formula 1 wherein

R<sub>1</sub> is hydrogen, hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy or free or esterified or amidareal carboxy-lower alkoxy;

R<sub>2</sub> is hydrogen, lower alkyl, cycloalkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, hydroxy, optionally lower alkanoylated, halogenated or sulfonylated hydroxy-lower alkoxy; amino-lower alkyl that is unsubstituted or substituted by lower alkyl, by lower alkanoyl and/or by lower alkoxycarbonyl; optionally hydrogenated heteroaryl-lower alkyl; amino-lower alkoxy that is substituted by lower alkyl, by lower alkanoyl and/or by lower alkoxycarbonyl; oxo-lower alkoxy, lower alkoxy, cycloalkoxy, lower alkenyloxy, cycloalkoxy-lower alkoxy, lower alkoxy-lower alkoxy, lower alkoxy-lower alkenyl, lower alkenyloxy-lower alkoxy, lower alkoxy-lower alkenyloxy, lower alkenyloxy-lower alkyl, lower alkanoyl-lower alkoxy, optionally S-oxidised lower alkylthio-lower alkoxy, lower alkylthio-(hydroxy)-lower alkoxy, aryl-lower alkoxy, optionally hydrogenated heteroaryl-lower alkoxy, cyano-lower alkoxy, free or esterified or amidated carboxy-lower alkoxy or free or esterified or amidated carboxy-lower alkyl;

R<sub>3</sub> is optionally halogenated lower alkyl, lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, hydroxy-lower alkyl, optionally S-oxidised lower alkylthio-lower alkyl, optionally hydrogenareal heteroarylthio-lower alkyl, optionally hydrogenated heteroaryl-lower alkyl; amino-lower alkyl that is unsubstituted or N-mono- or N,N-di-lower

alkylated, N-lower alkanoylated or N-lower  
alkanesulfonylated or N,N-disubstituted by lower alkylene,  
by unsubstituted or N'-lower alkylated or N'-lower  
alkanoylated aza-lower alkylene, by oxa-lower alkylene or  
5 by optionally S-oxidised thia-lower alkylene; cyano-lower  
alkyl, free or esterified or amidated carboxy-lower alkyl,  
cycloalkyl, aryl, hydroxy, lower alkoxy, cycloalkoxy, lower  
alkoxy-lower alkoxy, cycloalkoxy-lower alkoxy, hydroxy-  
lower alkoxy, aryl-lower alkoxy, optionally halogenated  
10 lower alkoxy, optionally S-oxidised lower alkylthio-lower  
alkoxy, optionally hydrogenated heteroaryl-lower alkoxy,  
optionally hydrogenated heteroarylthio-lower alkoxy; amino-  
lower alkoxy that is unsubstituted or N-mono- or N,N-di-  
lower alkylated, N-lower alkanoylated or N-lower  
15 alkanesulfonylated or substituted by lower alkylene, by  
unsubstituted or N'-lower alkylated or N'-lower  
alkanoylated aza-lower alkylene, by oxa-lower alkylene or  
by optionally S-oxidised thia-lower alkylene; cyano-lower  
alkoxy or free or esterified or amidated carboxy lower  
20 alkoxy; or  
R<sub>3</sub> together with R<sub>4</sub> is lower alkylenedioxy or a fused-on benzo  
or cyclohexeno ring;  
R<sub>4</sub> together with R<sub>3</sub> is lower alkylenedioxy or a fused-on benzo  
or cyclohexeno ring, or is hydrogen, lower alkyl, hydroxy,  
25 lower alkoxy or cycloalkoxy;  
X is methylene or hydroxymethylene;  
R<sub>5</sub> is lower alkyl or cycloalkyl;  
R<sub>6</sub> is unsubstituted or N-mono- or N,N-di-lower alkylated or N-  
lower alkanoylated amino;  
30 R<sub>7</sub> is lower alkyl; lower alkenyl, cycloalkyl or aryl-lower  
alkyl; and  
R<sub>8</sub> is lower alkyl, cycloalkyl, free or aliphatically esterideal  
or etherideal hydroxy-lower alkyl; amino-lower alkyl that

is unsubstituted or N-lower alkanoylated or N-mono- or N,N-di-lower alkylated or N,N-disubstituted by lower alkylene, by hydroxy-, lower alkoxy- or lower alkanoyloxy-lower alkylene, by unsubstituted or N'-lower alkanoylated or N'-lower alkylated aza-lower alkylene, by oxa-lower alkylene or by optionally S-oxidised thia-lower alkylene; free or esterified or amidated carboxy-lower alkyl, free or esterified or amidated dicarboxy-lower alkyl, free or esterified or amidated carboxy-(hydroxy)-lower alkyl, free or esterified or amidated carboxycycloalkyl-lower alkyl, cyano-lower alkyl, lower alkanesulfonyl-lower alkyl, unsubstituted or N-mono- or N,N-di-lower alkylated thiocarbamoyl-lower alkyl, unsubstituted or N-mono- or N,N-di-lower alkylated sulfamoyl-lower alkyl, or a heteroaryl radical bonded via a carbon atom and optionally hydrogenated and/or oxo-substituted, or lower alkyl substituted by a heteroaryl radical bonded via a carbon atom and optionally hydrogenated and/or oxo-substituted, and to the salts thereof, to processes for the preparation of the compounds according to the invention, to pharmaceutical compositions containing them, and to their use as medicinal active ingredients.

In another aspect, the invention relates to a method using a compound of formula 1 wherein:

R<sub>1</sub> is hydrogen, hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy, carboxy-lower alkoxy, lower alkoxy-carbonyl-lower alkoxy, carbamoyl-lower alkoxy or N-mono- or N,N-di-lower alkylcarbamoyl-lower alkoxy;

R<sub>2</sub> is hydrogen, lower alkyl, cycloalkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, hydroxy, lower alkanoyloxy-lower alkyl, hydroxy-lower alkoxy, halo-(hydroxy)-lower alkoxy, lower

alkane-sulfonyl-(hydroxy)-lower alkoxy, amino-lower alkyl,  
lower alkylamino-lower alkyl, di-lower alkylamino-lower  
alkyl, lower alkanoylamino-lower alkyl, lower  
alkoxycarbonylamino-lower alkyl, amino-lower alkoxy, lower  
5 alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy,  
lower alkanoylamino-lower alkoxy, lower  
alkoxycarbonylamino-lower alkoxy, oxo-lower alkoxy, lower  
alkoxy, cycloalkoxy, lower alkenyloxy, cycloalkoxy-lower  
alkoxy, lower alkoxy-lower alkoxy, lower alkoxy-lower  
10 alkenyl, lower alkenyloxy-lower alkoxy, lower alkoxy-lower  
alkenyloxy, lower alkenyloxy-lower alkyl, lower alkanoyl-  
lower alkoxy, lower alkylthio-lower alkoxy, lower  
alkanesulfonyl-lower alkoxy, lower alkylthio-(hydroxy)-  
lower alkoxy, aryl-lower alkoxy, thiazolylthio-lower alkoxy  
15 or thiazolinylthio-lower alkoxy, imidazolylthio-lower  
alkoxy, optionally N-oxidised pyridylthio-lower alkoxy,  
pyrimidinylthio-lower alkoxy, cyano-lower alkoxy, lower  
alkoxycarbonyl-lower alkoxy, carbamoyl-lower alkoxy, N-  
mono- or N, N-all-lower alkylcarbamoyl-lower alkoxy,  
20 carboxy-lower alkyl, lower alkoxy-carbonyl-lower alkyl,  
carbamoyl-lower alkyl or N-mono- or N,N-di-lower alkyl-  
carbamoyl-lower alkyl;

R<sub>3</sub> is lower alkyl, polyhalo-lower alkyl, lower alkoxy-lower  
alkyl, cycloalkoxy-lower alkyl, hydroxy-lower alkyl, lower  
25 alkylthio-lower alkyl, lower alkanesulfonyl-lower alkyl,  
optionally partially hydrogenated or N-oxidised pyridyl-  
lower alkyl, thiazolylthio-lower alkyl or thiazolinylthio-  
lower alkyl, imidazolylthio-lower alkyl, optionally N-  
oxidised pyridylthio-lower alkyl, pyrimidinylthio-lower  
30 alkyl, amine-lower alkyl, lower alkylamino-lower alkyl, di-  
lower alkylamino-lower alkyl, lower alkanoylamino-lower  
alkyl, lower alkanesulfonylamino-lower alkyl, polyhalo-  
lower alkanesulfonylamino-lower alkyl, pyrrolidino-lower

alkyl, piperidino-lower alkyl, piperazino-, N'-lower  
alkylpiperazino- or N'-lower alkanoylpiperazino-lower  
alkyl, morpholino-lower alkyl, thiomorpholino-. S-  
oxothiomorpholino- or S,S-dioxothiomorpholino-lower alkyl,  
5 cyano-lower alkyl, carboxy-lower alkyl, lower  
alkoxycarbonyl-lower alkyl, carbamoyl-lower alkyl, N-mono-  
or N,N-di-lower alkylcarbamoyl-lower alkyl, cycloalkyl;  
phenyl or naphthyl that is unsubstituted or mono-, di- or  
tri-substituted by lower alkyl, lower alkoxy, hydroxy,  
10 lower alkylamino, di-lower alkylamino, halogen and/or by  
trifluoromethyl; hydroxy, lower alkoxy, cycloalkoxy, lower  
alkoxy-lower alkoxy, cycloalkoxy-lower alkoxy, hydroxy-  
lower alkoxy; phenyl-lower alkoxy or naphthyl-lower alkoxy  
that is unsubstituted or mono-, di- or tri-substituted by  
15 lower alkyl, lower alkoxy, hydroxy, lower alkylamino, di-  
lower alkylamino, halogen and/or by trifluoromethyl; lower  
alkoxy, polyhalo-lower alkoxy, lower alkylthio-lower  
alkoxy, lower alkanesulfonyl-lower alkoxy, optionally  
hydrogenated heteroaryl-lower alkoxy, optionally partially  
20 or fully hydrogenated hetero-arylthio-lower alkoxy, such as  
thiazolylthio-lower alkoxy or thiazolinythio-lower alkoxy,  
imidazolylthio-lower alkoxy, optionally N-oxidised  
pyridylthio-lower alkoxy, pyrimidinylthio-lower alkoxy,  
amine-lower alkoxy, lower alkylamino-lower alkoxy, di-lower  
25 alkylamino-lower alkoxy, lower alkanoylamino-lower alkoxy,  
lower alkanesulfonylamino-lower alkoxy, polyhalo-lower  
alkanesulfonylamino-lower alkoxy, pyrrolidino-lower alkoxy,  
piperidino-lower alkoxy, piperazino-, N'-lower  
alkylpiperazino- or N'-lower alkanoylpiperazino-lower  
30 alkoxy, morpholino-lower alkoxy, thiomorpholino-, S-  
oxothiomorpholino-or S,S-dioxothiomorpholino-lower alkoxy,  
cyano-lower alkoxy, carboxy-lower alkoxy, lower

alkoxycarbonyl-lower alkoxy, carbamoyl-lower alkoxy or N-mono- or N,N-di-lower alkylcarbamoyl-lower alkoxy;

R<sub>4</sub> is hydrogen, lower alkyl, hydroxy, lower alkoxy or cycloalkoxy;

5 X is methylene;

R<sub>5</sub> is lower alkyl or cycloalkyl;

R<sub>6</sub> is amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino;

10 R<sub>7</sub> is lower alkyl, lower alkenyl, cycloalkyl, or phenyl- or naphthyl-lower alkyl that is unsubstituted or mono-, di- or tri-substituted by lower alkyl, lower alkoxy, hydroxy, lower alkylamino, di-lower alkylamino, halogen and/or by trifluoromethyl; and

15 R<sub>8</sub> is lower alkyl, cycloalkyl, hydroxy-lower alkyl, lower alkanoyloxy-lower alkyl, lower alkoxy-lower alkyl or lower alkenyloxy-lower alkyl, amino-lower alkyl, lower alkanoylamino-lower alkyl N-mono- or N,N-di-lower alkylamino-lower alkyl, optionally hydroxylated or lower alkoxyated piperidino-lower alkyl, such as piperidino-lower alkyl, hydroxypiperidino-lower alkyl or lower alkoxy-piperidino-lower alkyl, piperazino-, N'-lower alkylpiperazino- or N'-lower alkanoylpiperazino-lower alkyl, unsubstituted or lower alkylated morpholino-lower alkyl, such as morpholino-lower alkyl or  
25 dimethylmorpholino-lower alkyl, or optionally S-oxidised thiomorpholino-lower alkyl, such as thiomorpholino-lower alkyl, S,S-dioxothiomorpholino-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, carbamoyl-lower alkyl, N-mono- or N,N-di-lower alkylcarbamoyl-lower alkyl,  
30 dicarboxy-lower alkyl, di-lower alkoxycarbonyl-lower alkyl, dicarbamoyl-lower alkyl, di-(N-mono- or N,N-di-lower alkylcarbamoyl)-lower alkyl, carboxy-(hydroxy)-lower alkyl, lower alkoxy-carbonyl-(hydroxy)-lower alkyl or carbamoyl-

(hydroxy)-lower alkyl, cyano-lower alkyl, lower alkanesulfonyl-lower alkyl, sulfamoyl-lower alkyl, lower alkyl-sulfamoyl-lower alkyl, di-lower alkylsulfamoyl-lower alkyl, thiocarbamoyl-lower alkyl, lower alkylthiocarbamoyl-lower alkyl, di-lower alkylthiocarbamoyl-lower alkyl, pyrrolidinyl, imidazolyl, benzimidazolyl, oxadiazolyl, pyridyl, oxopiperidinyl, quinolinyl, unsubstituted or N-lower alkanoylated piperidyl or pyrrolidinyl, imidazolyl-lower alkyl, benzimidazolyl-lower alkyl, oxadiazolyl-lower alkyl, pyridyl-lower alkyl, unsubstituted or N-lower alkanoylated piperidyl-lower alkyl or pyrrolidinyl-lower alkyl, oxopiperidinyl-lower alkyl, quinolinyl-lower alkyl, morpholinocarbonyl-lower alkyl or unsubstituted or N-lower alkanoylated piperidyl-lower alkyl, or a pharmaceutically acceptable salt thereof. .

In another aspect, the invention relates to a method using a compound of formula 1 wherein:

R<sub>1</sub> is hydrogen;

R<sub>2</sub> is lower alkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkoxy, lower alkoxy-tower alkoxy-lower alkyl; phenyl-lower alkoxy that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen, nitro and/or by amino; optionally N-oxidised pyridyl-lower alkoxy, lower alkylthio-lower alkoxy, lower alkanesulfonyl-lower alkoxy, lower alkanoyl-lower alkoxy, optionally N-oxidised pyridyl-lower alkoxy, cyano-lower alkoxy, carboxy-lower alkoxy, lower alkoxycarbonyl-lower alkoxy, carbamoyl-lower alkoxy, lower alkylcarbamoyl-lower alkoxy or di-lower alkylcarbamoyl-lower alkoxy,

R<sub>3</sub> is hydrogen, lower alkyl, hydroxy, lower alkoxy or polyhalo-lower alkoxy,

R<sub>4</sub> is hydrogen or together with R<sub>3</sub> is lower alkylidenedioxy,

X is methylene,

R<sub>5</sub> is lower alkyl or cycloalkyl;

R<sub>6</sub> is amine, lower alkylamino, di-lower alkylamino or lower alkanoylamino,

5 R<sub>7</sub> is lower alkyl, and

R<sub>8</sub> is lower alkyl, hydroxy-lower alkyl, lower alkanoyl-lower alkyl, lower alkoxy-lower alkyl, lower alkenyloxy-lower alkyl, amino-lower alkyl, lower alkanoyl-amino-lower alkyl, such as 2-(C<sub>1</sub>-C<sub>4</sub> alkanoylamino)-2-methyl-propyl, such as 2-  
10 acetyl-amino-2-methyl-propyl or 2-formyl-amino-2-methyl-propyl, N-mono- or N,N-di-lower alkylamino-lower alkyl, piperidino-lower alkyl, hydroxypiperidino-lower alkyl, lower alkoxypiperidino-lower alkyl, morpholino-lower alkyl, dimethylmorpholino-lower alkyl, thiomorpholino-lower alkyl.  
15 S,S-dioxothiomorpholino-lower alkyl, Carboxy-lower alkyl, lower alkoxy-carbonyl-lower alkyl, carbamoyl-lower alkyl, N-mono- or N,N-di-lower alkylcarbamoyl-lower alkyl, carboxy-(hydroxy)-lower alkyl, lower alkoxy-carbonyl-(hydroxy)-lower alkyl, carbamoyl-(hydroxy)-lower alkyl, 5- or 6-membered  
20 carboxycycloalkyl-lower alkyl, 5- or 6-membered lower alkoxy-carbonylcycloalkyl-lower alkyl. 5- or 6-membered carbamoylcycloalkyl-lower alkyl, 5- or 6-membered N-mono- or N, N-di-lower alkylcarbamoylcycloalkyl-lower alkyl, cyano-lower alkyl, lower alkanesulfonyl-lower alkyl,  
25 sulfamoyl-lower alkyl, lower alkylsulfamoyl-lower alkyl or di-lower alkylsulfamoyl-lower alkyl, imidazolyl-lower alkyl, oxopyrrolidinyl-lower alkyl, benzimidazolyl-lower alkyl, oxadiazolyl-lower alkyl, pyridyl-lower alkyl, oxopiperidinyl-lower alkyl or quinolinyl-lower alkyl,  
30 piperidin-4-yl-lower alkyl or 1-C<sub>1</sub> -C<sub>7</sub> -lower alkanoylpiperidin-4-yl-lower alkyl, or a pharmaceutically acceptable salt thereof. .



In another aspect, the invention relates to a method using a compound of formula 1 wherein:

R<sub>1</sub> and R<sub>4</sub> are hydrogen;

R<sub>2</sub> is C<sub>1</sub>-C<sub>4</sub> alkoxy- C<sub>1</sub>-C<sub>4</sub> alkoxy or C<sub>1</sub>-C<sub>4</sub> alkoxy- C<sub>1</sub>-C<sub>4</sub> alkyl;

5 R<sub>3</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> alkoxy;

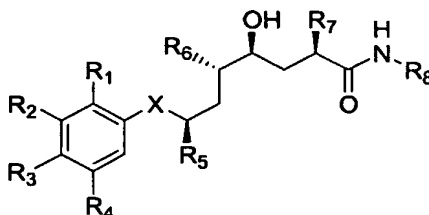
R<sub>6</sub> is amino;

X is methylene;

R<sub>5</sub> and R<sub>7</sub> are branched C<sub>1</sub>-C<sub>4</sub> alkyl; and

10 R<sub>8</sub> is carbamoyl- C<sub>1</sub>-C<sub>4</sub> alkyl, N-C<sub>1</sub>-C<sub>4</sub> alkylcarbamoyl- C<sub>1</sub>-C<sub>4</sub> alkyl, N,N-di- C<sub>1</sub>-C<sub>4</sub> alkyl-carbamoyl- C<sub>1</sub>-C<sub>4</sub> alkyl, morpholino- C<sub>1</sub>-C<sub>4</sub> alkyl, thiomorpholino- C<sub>1</sub>-C<sub>4</sub> alkyl, 4-(1- C<sub>1</sub>-C<sub>4</sub> alkanoylpiperidyl)- C<sub>1</sub>-C<sub>4</sub> alkyl or 2-oxopyrrolidinyl- C<sub>1</sub>-C<sub>4</sub> alkyl, or a pharmaceutically acceptable salt thereof. .

15 In another aspect, the invention relates to a method using a compound of formula 1 wherein at least one asymmetric carbon atom of the main chain has the stereochemical configuration shown in formula 1a



20 formula 1a

each of the variables being as defined in claim 1, or a pharmaceutically acceptable salt thereof.

Representative compounds of the invention include:

25 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(p-tert-butyl-phenyl)-octanoic acid (N-butyl)amide;

2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-ethyl-8-(p-tert-butyl-phenyl)-octanoic acid (N-butyl)amide;

2 (R,S) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -methyl-8- (4-biphenyl-octanoic acid (N-butyl) amide;

2 (R) -methyl-4 (S) -hydroxy-5 (S) -amine-7 (S) -isopropyl-8- (3-hydroxy-4-tert-butyl-phenyl) -octanoic acid (N-butyl) amide;

5 2 (R,S) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- (2-hydroxy-4-tert-butyl-phenyl) -octanoic acid (N-butyl) amide;

2 (R) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- (3-ethoxycarbonylmethoxy-4-tert-butyl-phenyl) -octanoic acid (N-butyl) amide;

10 2 (R) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- (3-allyloxy-4-tert-butyl-phenyl) -octanoic acid (N-butyl) amide;

2 (R,S) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- (3-methoxycarbonyl-allyloxy-4-tert-butyl-phenyl) -octanoic acid (N-butyl) amide;

15 2 (R,S) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- (3-methoxycarbonyl-methoxy-4-tert-butyl-phenyl) -octanoic acid (N-butyl) amide;

2 (R,S) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- (3-carbamoyl-methoxy-4-tert-butyl-phenyl) -octanoic acid (N-butyl) amide;

20 2 (R,S) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3-(pyrid-2-yl-methoxy) -4-tert-butyl-phenyl] -octanoic acid (N-butyl) amide;

2 (R,S) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3-(pyrid-4-yl-methoxy) -4-tert-butyl-phenyl] -octanoic acid (N-butyl) amide;

2 (R,S) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3-(N-oxido-pyrid-2-yl-methoxy) -4-tert-butyl-phenyl] -octanoic acid (N-butyl) amide;

30 2 (R,S) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3-(2-ethoxycarbonyl allyl-oxy) -4-tert-butyl-phenyl] -octanoic acid (N-butyl) amide;

2 (R,S)-methyl-4 (S)-hydroxy-5 (S)-amino-7 (S)-isopropyl-8-[3-(2-ethoxycarbonyl-propyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl) amide;

5 2 (R,S)-methyl-4 (S)-hydroxy-5 (S)-amino-7 (S)-isopropyl-8-[3-(methylthio-methoxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl) amide;

2 (R,S)-methyl-4 (S)-hydroxy-5 (S)-amino-7 (S)-isopropyl-8-[3-(methylsulfonyl-methoxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl) amide;

10 2 (R,S)-methyl-4 (S)-hydroxy-5 (S)-amino-7 (S)-isopropyl-8-[3-(carboxy-methoxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl) amide;

2 (R,S)-methyl-4 (S)-hydroxy-5 (S)-amino-7 (S)-isopropyl-8-[3-(3,3-dimethyl-2-oxo-butyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl) amide;

15 2 (R,S)-methyl-4 (S)-hydroxy-5 (S)-amino-7 (S)-isopropyl-8-[3-(2-nitrobenzyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl) amide;

2 (R,S)-methyl-4 (S)-hydroxy-5 (S)-amino-7 (S)-isopropyl-8-[3-(2-aminobenzyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl) amide;

2 (R,S)-methyl-4 (S)-hydroxy-5 (S)-amino-7 (S)-isopropyl-8-[3-(3-chloro-2 (R)-hydroxypropyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl) amide;

25 2 (R,S)-methyl-4 (S)-hydroxy-5 (S)-amino-7 (S)-isopropyl-8-[3-(3-methylthio-2 (S,R)-hydroxypropyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl) amide;

2 (R,S)-methyl-4 (S)-hydroxy-5 (S)-amino-7 (S)-isopropyl-8-[3-(3-methylsulfonyl-(S,R)-hydroxypropyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl) amide;

30 2 (R)-methyl-4 (S)-hydroxy-5 (S)-amino-7 (S)-isopropyl-8-[3-(methylsulfonyl-methoxy)-4-tert-butyl-phenyl]-octanoic acid (N-3-morpholino-propyl) amide;

2 (R) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- (3-methoxycarbonyl-methoxy-phenyl) -octanoic acid (N-butyl) amide;

2 (R) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3-(methoxycarbonyl-methoxy) -4-methoxy-phenyl] -octanoic acid (N-  
5 butyl) amide;

2 (R) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3- (N-methyl-carbamoyl-methoxy) -4-methoxy-phenyl] -octanoic acid (N-butyl) amide;

2 (R) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3- (3-methylsulfonyl-propyloxy) -4-methoxy-phenyl] -octanoic acid (N-  
10 butyl) amide;

2 (R) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3- (methylsulfonyl-methoxy) -4-methoxy-phenyl] -octanoic acid (N-butyl) amide;

15 2 (R) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3- (3-methoxy-propyloxy) -4-methoxy-phenyl] -octanoic acid (N-butyl) amide;

2 (R) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3- (2-methoxy-ethoxy) - 4-methoxy-phenyl] -octanoic acid (N-butyl) amide;

20 2 (R) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3- (3-hydroxy-propyloxy) -4-methoxy-phenyl] -octanoic acid (N-butyl) amide;

2 (R) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3- (carbamoylmethoxy) -4-methoxy-phenyl] -octanoic acid (N-  
25 butyl) amide;

2 (R) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- (3-cyanomethoxy-4-methoxy-phenyl) -octanoic acid (N-butyl) amide;

2 (R) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3- (4-methoxy-butoxy) -4-methoxy-phenyl] -octanoic acid (N-butyl) amide;

30 2 (R) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3- (2-ethoxy-ethoxy) -4-methoxy-phenyl] -octanoic acid (N-butyl) amide;

2 (R) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- {3- [2-  
(2-methoxy-ethoxy) -ethoxy] -4-methoxy-phenyl} -octanoic acid (N-  
butyl) amide;

2 (R) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- (3-  
5 pentyloxy-4-methoxy -phenyl) -octanoic acid (N-butyl) amide;

2 (R) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- (3-  
benzyloxy-4-methoxy -phenyl) -octanoic acid (N-butyl) amide;

2 (R) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3- (3-  
ethoxy-propyloxy) -4-methoxy-phenyl] -octanoic acid (N-butyl) amide;

10 2 (R) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3-  
(pyrid-4-ylmethoxy) -4-methoxy-phenyl] -octanoic acid (N-  
butyl) amide;

2 (R, S) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- (2-  
ethoxycarbonyl-methoxy-4-tert-butyl-phenyl) -octanoic acid (N-  
15 butyl) amide;

2 (R, S) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- (2-  
ethoxycarbonyl-4-tert-butyl-phenyl) -octanoic acid (N-  
butyl) amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4- (3-  
20 hydroxypropyloxy) -3- (3-methoxy-propyloxy) -phenyl] -octanoic acid  
[N- (2-carbamoyl-2,2-dimethyl-ethyl)] -amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-  
isopropyl-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (2-  
carbamoyl-2,2-dimethyl-ethyl)] -amide;

25 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-tert-  
butyl-3- (3-methoxy-propyl-oxy) -phenyl] -octanoic acid [N- (2-  
carbamoyl-2,2-dimethyl-ethyl)] -amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4- (3-  
methylsulfonyl-propyloxy) -3- (3-methoxy-propyloxy) -phenyl] -  
30 octanoic acid (N-2-morpholinoethyl) amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4- (3-  
methylsulfonyl-propyloxy) -3- (3-methoxy-propyloxy) -phenyl] -  
octanoic acid [N- (2-carbamoyl-2,2-dimethyl-ethyl)] -amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [3,4-di (3-hydroxypropyloxy) -phenyl] -octanoic acid (N-2-morpholinoethyl) amide;

5 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [3,4-di (3-hydroxypropyloxy) -phenyl] -octanoic acid [N- (2-carbamoyl-2,2-dimethyl-ethyl)] -amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4- (3-N-methylcarbamoyl-propyl) -3- (3-methoxy-propyloxy) -phenyl] -octanoic acid (N-2-morpholinoethyl) amide;

10 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4- (2-morpholinoethoxy) -3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (2-carbamoyl-2,2-dimethyl-ethyl)] -amide;

15 [5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [3- (3-methoxypropyloxy) -4,5-ethylenedioxy-phenyl] -octanoic acid (N-2-morpholinoethyl) amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [3- (3-methoxypropyloxy) -4,5-ethylenedioxy-phenyl] -octanoic acid [N- (2-carbamoyl-2,2-dimethyl-ethyl)] -amide;

20 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [3- (3-methoxy-propyloxy) -4,5-methylenedioxy-phenyl] -octanoic acid (N-2-morpholinoethyl) amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [3- (3-methoxypropyloxy) -4,5-methylenedioxy-phenyl] -octanoic acid [N- (2-carbamoyl-2,2-dimethyl-ethyl)] amide;]

25 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (2-carbamoyl-2,2-ethylene-ethyl)] -amide;

30 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propoxy) -phenyl] -octanoic acid [N- (3 (S) -2-oxo-pyrrolidin-3-yl-methyl)] amide;

5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- [4-methoxy-3- (4-methoxy-but-2-eneoxy) -phenyl] -octanoic acid (N-butyl) amide;

5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- [4-  
hydroxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid (N-  
butyl) amide;

5 5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8-H-  
benzyloxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid (N-  
butyl) amide;

5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- [3, 4-  
di (3-methoxypropyloxy) -phenyl] -octanoic acid (N-butyl) amide;

10 5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- [4-  
(2,2,2-trifluoroethoxy) -3- (3-methoxypropyloxy) -phenyl] -octanoic  
acid (N-butyl) amide;

5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- [4- (3-  
hydroxy-propyloxy) -3- (3-methoxypropyloxy) -phenyl] -octanoic acid  
(N-butyl) amide;

15 5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- [4- (2-  
amino-ethoxy) -3- (3-methoxypropyloxy) -phenyl] -octanoic acid (N-  
butyl) amide;

5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- [4- (5-  
amino-pentyloxy) -3- (3-methoxypropyloxy) -phenyl] -octanoic acid  
20 (N-butyl) amide;

5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- [4- (4-  
amino-butyloxy) -3- (3-methoxypropyloxy) -phenyl] -octanoic acid (N-  
butyl) amide;

25 5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- [4- (4-  
N,N-dimethylamino-butyloxy) -3- (3-methoxypropyloxy) -phenyl] -  
octanoic acid (N-butyl) amide;

5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- {4- [4-  
N- (trifluoromethane-sulfonylaminobutyloxy) -3- (3-  
methoxypropyloxy) -phenyl] } -octanoic acid (N-butyl) -amide;

30 5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- [4-  
carboxymethoxy-3- (3-methoxypropyloxy) -phenyl] -octanoic acid (N-  
butyl) amide;

5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- [4- (3-ethoxycarbonyl-propyloxy) -3- (3-methoxy-propyloxy) -phenyl] -octanoic acid (N-butyl) amide;

5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- [4- (3-carboxy-propyloxy) -3- (3-methoxypropyloxy) -phenyl] -octanoic acid (N-butyl) amide;

5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- [4- (4-methoxycarbonylbutyloxy) -3- (3-methoxypropyloxy) -phenyl] -octanoic acid (N-butyl) amide;

10 5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- [4- (4-carboxy-butyloxy) -3- (3-methoxypropyloxy) -phenyl] -octanoic acid (N-butyl) amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid (N-butyl) amide;

15 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (2-methoxymethoxy-ethyl) -phenyl] -octanoic acid (N-butyl) amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4- (3-hydroxypropyloxy) -3- (methoxypropyloxy) -phenyl] -octanoic acid N- (2-morpholinoethyl) amide;

20 5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- [2- (4-hydroxypiperidin-1-yl) ethyl] amide dihydrochloride;

5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- [2- (trans-2,6-dimethyl-morpholino ) ethyl] amide;

25 5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- [4-methoxy-3- (3-methoxypropyloxy) -phenyl] -octanoic acid N- [2- (cis-2,6-dimethyl-morpholino) ethyl] amide;

30 5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- (2-piperidinoethyl) amide;



5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8 - [4-methoxy-3 - (3-methoxy-propyloxy) -phenyl] -octanoic acid N - [2 - (4-methoxypiperidino) -ethyl] -amide;

5 5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8 - [4-methoxy-3 - (3-methoxy-propyloxy) -phenyl] -octanoic acid N - (2-thiomorpholinoethyl) amide;

5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8 - [4-methoxy-3 - (3-methoxy-propyloxy) -phenyl] -octanoic acid [N - (3-hydroxypropyl)] amide;

10 5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8 - [4-methoxy-3 - (3-methoxy-propyloxy) -phenyl] -octanoic acid [N - (4-acetoxybutyl)] amide;

15 5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8 - [4-methoxy-3 - (3-methoxy-propyloxy) -phenyl] -octanoic acid [N - (3-cyanopropyl)] amide;

5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8 - [4-methoxy-3 - (3-methoxy-propyloxy) -phenyl] -octanoic acid [N - (3-methoxypropyl)] amide;

20 5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8 - [4-methoxy-3 - (3-methoxy-propyloxy) -phenyl] -octanoic acid [N - (2-acetyl-amino-ethyl)] amide;

5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8 - [4-methoxy-3 - (3-methoxy-propyloxy) -phenyl] -octanoic acid {N - [2 - (2-pyridyl) -ethyl]} amide;

25 5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8 - [4-methoxy-3 - (3-methoxy-propyloxy) -phenyl] -octanoic acid N - [2 - (N-oxomorpholino) ethyl] amide;

30 5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8 - [4-methoxy-3 - (3-methoxy-propyloxy) -phenyl] -octanoic acid {N - [3 - (tert-butylsulfonyl) -propyl]} amide;

5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8 - [4-methoxy-3 - (3-methoxy-propyloxy) -phenyl] -octanoic acid {N - [3 - (ethylsulfonyl) -propyl]} -amide;

5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8 - [4-methoxy-3 - (3-methoxy-propyloxy) -phenyl] -octanoic acid {N - [2 - (ethylsulfonyl) -ethyl] } -amide;

5 5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8 - [4-methoxy-3 - (3-methoxy-propyloxy) -phenyl] -octanoic acid {N - [2 - (N-butylsulfonyl) -ethyl] } -amide;

[ (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8 - [4-methoxy-3 - (3-methoxy-propyloxy) -phenyl] -octanoic acid {N - [2 - (N,N-dimethylsulfonylamino) -ethyl] } -amide;

10 5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8 - [4-methoxy-3 - (3-methoxy-propyloxy) -phenyl] -octanoic acid {N - [3 - (1H-tetrazol-5-yl) -propyl] } -amide;

15 5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8 - [4-methoxy-3 - (3-methoxy-propyloxy) -phenyl] -octanoic acid {N - [3 - (1H-imidazol-5-yl) -propyl] } -amide;

5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8 - [4-methoxy-3 - (3-methoxy-propyloxy) -phenyl] -octanoic acid {N - [3 - (3-methyl-1,2,4-oxadiazol-5-yl) -propyl] } -amide;

20 5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8 - [4-methoxy-3 - (3-methoxy-propyloxy) -phenyl] -octanoic acid [N - (3-aminopropyl) ] -amide;

5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8 - [4-methoxy-3 - (3-methoxy-propyloxy) -phenyl] -octanoic acid [N - [2 - dimethylamino-ethyl] ] -amide;

25 5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8 - [4-methoxy-3 - (3-methoxy-propyloxy) -phenyl] -octanoic acid N - (2-morpholinoethyl) amide;

30 5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8 - [4-methoxy-3 - (3-methoxy-propyloxy) -phenyl] -octanoic acid N - (3-morpholinopropyl) amide;

5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8 - [4-methoxy-3 - (3-methoxy-propyloxy) -phenyl] -octanoic acid N - [2 - (1,1-dioxothiomorpholino) ethyl] amide;

5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- (2-ethoxycarbonyl-ethyl) amide;

5 5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (2-carboxy-ethyl)] -amide;

5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (3-methoxycarbonyl-ethyl)] -amide;

10 5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (3-carboxypropyl)] -amide;

15 5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (2-carbamoyl-ethyl)] -amide;

5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (4-carbamoyl-butyl)] -amide;

20 5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- {3- [N- (2-methoxyethyl) carbamoyl] propyl} amide;

5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- (4-morpholino-4-oxo-butyl) amide;

25 5 (S) -amino-4 (S) -hydroxy-7 (S) -isopropyl-2 (R) -methyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (2-carbamoyl-2,2-dimethyl-ethyl)] -amide;

30 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- (1,1 -dimethyl-2-morpholino-ethyl) amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- [1 (R, S) -methyl-2-morpholino-ethyl] amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (1 -carbamoyl-1-methyl-ethyl)] -amide;

5 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (1-carbamoyl-methyl)] -amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (2-carbamoyl-ethyl)] -amide;

10 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- [2- (N-methyl-carbamoyl) ethyl] amide;

15 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- (3-morpholino-3-oxo-propyl) amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid {N- [2- (N,N-dimethyl-carbamoyl) -1 (R,S) -methyl-ethyl]} -amide;

20 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (2-carbamoyl-1 (R) -isopropyl-ethyl)] -amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid {N- [2- (N-methylcarbamoyl) -1 (R) -isopropyl-ethyl]} -amide;

25 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid {N- [2- (N,N-dimethylcarbamoyl) -1 (R) -isopropyl-ethyl]} -amide;

30 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (1 (S) -carbamoyl-2-hydroxy-ethyl)] -amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (1 (S) , 2-dicarbamoyl-ethyl)] -amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (1 (S) , 3-dicarbamoyl-propyl) ] -amide;

5 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (1 (S) -carbamoyl-propyl) ] -amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (1 (S) -carbamoyl-2 (S) -methyl-butyl) ] -amide;

10 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- [2 (R, S) -carbamoyl-2 (R, S) -methyl-ethyl] -amide;

15 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (2-carbamoyl-1 (S) -methyl-ethyl) ] -amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (2-carbamoyl-1 (R) -methyl-ethyl) ] -amide;

20 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- [2 (S) -carbamoyl-2 (S) -methylethyl] -amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid {N- [2 (S) - (N-methyl-carbamoyl) -2 (S) -methyl-ethyl] } -amide;

25 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (2-carboxy-2, 2-dimethyl-ethyl) ] -amide;

30 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (2-carboxy-2, 2-diethyl-ethyl) ] -amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- [(1-carboxy-cyclopentyl) -methyl] amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid {N- [2- (1 H-tetrazol-5-yl) -ethyl] } -amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- [1 (S) - (5-oxopyrrolidin-2-yl) methyl] -amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- [1 (R) - (5-oxopyrrolidin-2-yl) methyl] -amide;

10 5 (S) -amine-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- [N- (morpholin-4-yl) carbamoyl-methyl] amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (1 (S) -carbamoyl-ethyl) ] -amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- {1 (S) - [ (N-methyl) -carbamoyl] -ethyl} -amide;

20 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- {1 (S) - [ (N, N-dimethyl) -carbamoyl] -ethyl} -amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- {1 (S) - N- [(morpholin-4-yl) -carbamoyl] -ethyl} amide;

25 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- [1 (S) - carbamoylbutyl] amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- [1 (S) - carbamoyl-2-methyl-propyl] -amide;

30 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- [1 (S) - (N-methylcarbamoyl) -2-methyl-propyl] amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- [1 (S) - (N,N-dimethylcarbamoyl) -2-methyl-propyl] amide;

5 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- {1 (S) - [N- (morpholin-4-yl) carbamoyl] -2-methyl-propyl} amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- [2- (N-methylsulfonylamino) ethyl] amide;

10 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- {2- [N- (morpholin-4-yl) -sulfonyl] ethyl} amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- [(N-acetyl-piperidin-4-yl) methyl] amide;

15 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (4-methoxy-butyl) -phenyl] -octanoic acid N- (2-carbamoyl-2,2-dimethylethyl) amide;

20 5 (S) , amino, 4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid N- [2- (N,N-dimethylcarbamoyl) ethyl] amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (4-methoxybutylphenyl) -octanoic acid N- (2-morpholinoethyl) amide; and a pharmaceutically salt thereof.

25

Other representative compounds of the invention include:

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (3 (R) -2-oxo-pyrrolidin-3-yl-methyl)] -amide;

30 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (3 (S) -2-oxo-piperidin-3-yl-methyl)] -amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (3 (R) -2-oxo-piperidin-3-yl-methyl)] -amide;

5 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyl-oxy) -phenyl] -octanoic acid [N- (3-carbamoyl-3,3-dimethyl-propyl)] -amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (4-methoxy-butyl) phenyl] -octanoic acid [N- (5 (S) -2-pyrrolidinon-5-yl-methyl)] -amide;

10 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (4-methoxy-butyl) -phenyl] -octanoic acid [N- (5 (R) -2-pyrrolidinon-5-yl-methyl)] -amide;

15 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (6 (S) -2-oxo-piperidin-6-yl-methyl)] -amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (6 (R) -2-oxo-piperidin-6-yl-methyl)] -amide;

20 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (2-thiazol-2-yl-ethyl)] -amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (4 (S) -2-oxazolidinon-4-yl-methyl)] -amide;

25 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (4 (R) -2-oxazolidinon-4-yl-methyl)] -amide;

30 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (3 (S) -2.5-dioxo-pyrrolidin-3-yl-methyl)] -amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (3 (R) -2.5-dioxo-pyrrolidin-3-yl-methyl)] -amide;



5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (2,6-dioxo-piperidin-4-yl-methyl)] -amide;

5 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (4 (S) -2-oxothiazolidin-4-yl-methyl)] -amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (4 (R) -2-oxothiazolidin-4-yl-methyl)] -amide;

10 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (tetrahydro-2-pyrimidon-5-yl-methyl)] -amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxypropyloxy) -phenyl] -octanoic acid [N- (N-acetyl-2-amino-2-methyl-propyl)] -amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (N-formyl-2-amino-2-methyl-propyl)] -amide;

20 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (4-acetyl-piperazinyl-ethyl)] -amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (2,4-imidazolinedion-5-yl-methyl)] -amide;

25 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (4-methoxy-butyl)phenyl] -octanoic acid [N- (2-hydroxy-pyridin-6-yl-methyl)] -amide;

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (2,2-dimethyl-2-sulfamoyl-ethyl)] -amide;

30 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (2,2-dimethyl-2- (N,N-dimethyl) -sulfamoyl-ethyl)] -amide;

5 (S)-amino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-oxo-piperidin-3 (R)-yl)]-amide;

5 5 (S)-amino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-oxo-piperidin-3 (S)-yl)]-amide;

5 (S)-amino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-oxo-piperidin-4-yl)]-amide;

10 5 (S)-amino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(N-acetyl-piperidin-4-yl)]-amide; or

5 (S)-amino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(4-methoxy-but-1 en-yl)-phenyl]-octanoic acid [N-(2-carbamoyl-15 2,2-dimethyl-ethyl)]-amide;

and pharmaceutically acceptable salts thereof.

In one aspect, the invention provides a method using a compound that is 5 (S)-Amino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-20 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid morpholinopropyl)amide or a pharmaceutically acceptable salt thereof.

In one aspect, the invention provides a method using a compound that is 5 (S)-Amino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-25 8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid morpholinoethyl)amide or a pharmaceutically acceptable salt thereof.

30 In one aspect, the invention provides a method using a compound that is 5 (S)-Amino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-

(N-methyl-carbamoyl)-1(R,S)-methyl-ethyl}-amide or a pharmaceutically acceptable salt thereof.

5 In one aspect, the invention provides a method using a compound that is 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(3-carbamoylpropyl)amide or a pharmaceutically acceptable salt thereof.

10 In one aspect, the invention provides a method using a compound that is 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2(R)-(N-methyl-carbamoyl)-2(R)-methyl-ethyl]}-amide or a pharmaceutically acceptable salt thereof.

15 In one aspect, the invention provides a method using a compound that is 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-thiomorpholinoethyl)amide or a pharmaceutically acceptable salt thereof.

20 In one aspect, the invention provides a method using a compound that is 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N,N-dimethyl-carbamoyl)ethyl]amide or a pharmaceutically acceptable salt thereof.

25 In one aspect, the invention provides a method using a compound that is 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoyl-1(R,S)-methyl-ethyl)amide or a pharmaceutically acceptable salt thereof.

In one aspect, the invention provides a method using a compound that is 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2(R)-carbamoyl-2(R)-methyl-ethyl]-amide or a pharmaceutically acceptable salt thereof.

In one aspect, the invention provides a method using a compound that is 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)amide or a pharmaceutically acceptable salt thereof.

In one aspect, the invention provides a method using a compound that is 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N-acetyl)-piperidin-4-yl)ethyl]amide or a pharmaceutically acceptable salt thereof.

In one aspect, the invention provides a method using a compound that is 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[(N,N-dimethyl)-carbamoyl-methyl]}-amide or a pharmaceutically acceptable salt thereof.

In one aspect, the invention provides a method using a compound that is 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2(R, S)-(N-methylcarbamoyl)-2(R,S)-methyl-ethyl]-amide or a pharmaceutically acceptable salt thereof.

In one aspect, the invention provides a method using a compound that is 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-

carbamoyl-2,2-dimethyl-ethyl)-amide or a pharmaceutically acceptable salt thereof.

5 In one aspect, the invention provides a method using a compound that is 5(S)-Amino-2(S),7(S)-diisopropyl-4(S)-hydroxy-8-[4-tert-butyl-3-(3-methoxypropoxy)-phenyl]-octanoic acid [N-2-(morpholin-4-yl)-ethyl]-amide or a pharmaceutically acceptable salt thereof.

10 In one preferred aspect, the invention provides a method for treating Alzheimer's or a related condition wherein the subject is a human.

15 In one aspect, the invention provides a method for treating Alzheimer's or a related condition wherein the disease is dementia.

20 In one aspect, the invention provides a method for treating alzheimers or a related condition wherein the disease is Alzheimer's disease.

**Definitions**

Aryl and aryl in aryl-lower alkoxy, aryl-lower alkyl and the like is, for example, phenyl or naphthyl that is unsubstituted or mono-, di- or tri-substituted by lower alkyl,  
5 lower alkoxy, hydroxy, lower alkylamino, di-lower alkylamino, halogen and/or by trifluoromethyl.

Cycloalkoxy and cycloalkoxy in cycloalkoxy-lower alkoxy is, for example, 3- to 8-membered, preferably 3-, 5- or 6-membered, cycloalkoxy, such as cyclopropyloxy, cyclopentyloxy,  
10 cyclohexyloxy, also cyclobutyloxy, cycloheptyloxy or cyclooctyloxy.

Cycloalkyl is, for example, 3- to 8-membered, preferably 3-, 5- or 6-membered, cycloalkyl, such as cyclopropyl, cyclopentyl, cyclohexyl, also cyclobutyl, cycloheptyl or  
15 cyclooctyl.

Free or esterified or amidated carboxy-lower alkoxy is, for example, carboxy-lower alkoxy, lower alkoxycarbonyl-lower alkoxy, carbamoyl-lower alkoxy or N-mono- or N,N-di-lower alkylcarbamoyl-lower alkoxy.

20 Optionally lower alkanoylated, halogenated or sulfonylated hydroxy-lower alkoxy is, for example, lower alkanoyloxy-lower alkyl, hydroxy-lower alkoxy, halo-(hydroxy)-lower alkoxy or lower alkanesulfonyl-(hydroxy)-lower alkoxy.

Amino-lower alkyl that is unsubstituted or substituted by  
25 lower alkyl, lower alkanoyl and/or by lower alkoxycarbonyl is, for example, amino-lower alkyl, lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, lower alkanoylamino-lower alkyl or lower alkoxycarbonylamino-lower alkyl.

Amino-lower alkoxy that is unsubstituted or substituted by  
30 lower alkyl, lower alkanoyl and/or by lower alkoxycarbonyl is, for example, amino-lower alkoxy, lower alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy, lower alkanoylamino-lower alkoxy or lower alkoxycarbonylamino-lower alkoxy.

Optionally S-oxidised lower alkylthio-lower alkoxy is, for example, lower alkylthio-lower alkoxy or lower alkanesulfonyl-lower alkoxy.

5      Optionally hydrogenated heteroaryl-lower alkoxy is, for example, optionally partially hydrogenated or N-oxidised pyridyl-lower alkoxy, thiazolyl-lower alkoxy or especially morpholino-lower alkoxy.

10      Optionally hydrogenated heteroarylthio-lower alkoxy is, for example, optionally partially or fully hydrogenareal heteroarylthio-lower alkoxy, such as thiazolylthio-lower alkoxy or thiazolinythio-lower alkoxy, imidazolylthio-lower alkoxy, optionally N-oxidised pyridylthio-lower alkoxy or pyrimidinylthio-lower alkoxy.

15      Free or esterified or amidated carboxy-lower alkyl is, for example, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, carbamoyl-lower alkyl or N-mono- or N,N-di-lower alkylcarbamoyl-lower alkyl.

Optionally halogenated lower alkyl is, for example, lower alkyl or polyhalo-lower alkyl.

20      Optionally halogenated lower alkoxy is, for example, lower alkoxy or polyhalo-lower alkoxy.

Optionally S-oxidised lower alkylthio-lower alkyl is, for example, lower alkylthio-lower alkyl or lower alkanesulfonyl-lower alkyl.

25      Optionally S-oxidised lower alkylthio-lower alkoxy is, for example, lower alkylthio-lower alkoxy or lower alkanesulfonyl-lower alkoxy.

30      Optionally hydrogenated heteroaryl-lower alkyl is, for example, optionally partially hydrogenated or N-oxidised pyridyl-lower alkyl.

Optionally hydrogenated heteroarylthio-lower alkyl is, for example, thiazolylthio-lower alkyl or thiazolinythio-lower

alkyl, imidazolylthio-lower alkyl, optionally N-oxidised pyridylthio-lower alkyl or pyrimidinylthio-lower alkyl.

Amino-lower alkyl that is unsubstituted or N-mono- or N,N-di-lower alkylated, N-lower alkanoylated or N-lower alkanesulfonylated or N,N-disubstituted by lower alkylene, by 5 unsubstituted or N'-lower alkylated or N'-lower alkanoylated aza-lower alkylene, by oxa-lower alkylene or by optionally S-oxidised thia-lower alkylene is, for example, amino-lower alkyl, lower alkylamino-lower alkyl, di-lower alkylamino-lower alkyl, 10 lower alkanoylamino-lower alkyl, lower alkanesulfonylamino-lower alkyl, polyhalo-lower alkanesulfonylamino-lower alkyl, pyrrolidino-lower alkyl, piperidino-lower alkyl, piperazino-, N'-lower alkylpiperazino- or N'-lower alkanoylpiperazino-lower alkyl, morpholino-lower alkyl, thiomorpholino-, S- 15 oxothiomorpholino- or S,S-dioxothiomorpholino-lower alkyl.

Optionally S-oxidised lower alkylthio-lower alkoxy is, for example, lower alkylthio-lower alkoxy or lower alkanesulfonyl-lower alkoxy.

Amino-lower alkoxy that is unsubstituted or N-mono- or N,N-di-lower alkylated, N-lower alkanoylated or N-lower alkanesulfonylated or N,N-disubstituted by lower alkylene, by 20 unsubstituted or N'-lower alkylated or N'-lower alkanoylated aza-lower alkylene, by oxa-lower alkylene or by optionally S-oxidised thia-lower alkylene is, for example, amino-lower alkoxy, lower alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy, 25 lower alkanoylamino-lower alkoxy, lower alkanesulfonylamino-lower alkoxy, polyhalo-lower alkanesulfonylamino-lower alkoxy, pyrrolidino-lower alkoxy, piperidino-lower alkoxy, piperazino-, N'-lower alkylpiperazino- 30 or N'-lower alkanoylpiperazino-lower alkoxy, morpholino-lower alkoxy, thiomorpholino-, S-oxothiomorpholino- or S,S-dioxothiomorpholino-lower alkoxy.



Unsubstituted or N-mono- or N,N-di-lower alkylated or N-lower alkanoylated amino is, for example, amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino.

Free or aliphatically esterified or etherified hydroxy-lower alkyl is, for example, hydroxy-lower alkyl, lower alkanoyloxy-lower alkyl, lower alkoxy-lower alkyl or lower alkenyloxy-lower alkyl.

Amino-lower alkyl that is unsubstituted or N-lower alkanoylated, N-mono- or N,N-di-lower alkylated or N,N-disubstituted by lower alkylene, by hydroxy-, lower alkoxy- or lower alkanoyloxy-lower alkylene, by unsubstituted or N'-lower alkanoylated aza-lower alkylene, by oxa-lower alkylene or by optionally S-oxidised thia-lower alkylene is, for example, amino-lower alkyl, lower alkanoylamino-lower alkyl, N-mono- or N,N-di-lower alkylamino-lower alkyl, optionally hydroxylated or lower alkoxyated piperidino-lower alkyl, such as piperidino-lower alkyl, hydroxypiperidino-lower alkyl or lower alkoxy-piperidino-lower alkyl, piperazino-, W-lower alkylpiperazino- or N'-lower alkanoyl-piperazino-lower alkyl, unsubstituted or lower alkylated morpholino-lower alkyl, such as morpholino-lower alkyl or dimethylmorpholino-lower alkyl, or optionally S-oxidised thio-morpholino-lower alkyl, such as thiomorpholino-lower alkyl or S,S-dioxothiomorpholino-lower alkyl.

Free or esterified or amidated dicarboxy-lower alkyl is, for example, dicarboxy-lower alkyl, di-lower alkoxycarbonyl-lower alkyl, dicarbamoyl-lower alkyl or di-(N-mono- or N,N-di-lower alkylcarbamoyl)-lower alkyl.

Free or esterified or amidated carboxy-(hydroxy)-lower alkyl is, for example, carboxy-(hydroxy)-lower alkyl, lower alkoxycarbonyl-(hydroxy)-lower alkyl or carbamoyl-(hydroxy)-lower alkyl.

Free or esterified or amidated carboxycycloalkyl-lower alkyl is, for example, 5- or 6-membered carboxycycloalkyl-lower

alkyl, lower alkoxy carbonylcycloalkyl-lower alkyl, carbamoylcycloalkyl-lower alkyl, or N-mono- or N,N-di-lower alkylcarbamoylcyclo-alkyl-lower alkyl.

Unsubstituted or N-mono- or N,N-di-lower alkylated  
5 sulfamoyl-lower alkyl is, for example, sulfamoyl-lower alkyl, lower alkylsulfamoyl-lower alkyl or di-lower alkyl-sulfamoyl-lower alkyl.

Unsubstituted or N-mono- or N,N-di-lower alkylated  
thiocarbamoyl-lower alkyl is, for example, thiocarbamoyl-lower  
10 alkyl, lower alkylthiocarbamoyl-lower alkyl or di-lower alkylthiocarbamoyl-lower alkyl, such as N,N-dimethylthiocarbamoylmethyl.

Heteroaryl that is optionally oxo-substituted, bonded via a carbon atom and optionally hydrogenated, and such a heteroaryl  
15 in a lower alkyl that is substituted by heteroaryl radicals that are optionally oxo-substituted, bonded via a carbon atom and optionally hydrogenated, contains as optionally hydrogenated heteroaryl radical, for example, an optionally partially hydrogenated and/or benzo-fused 5-membered aza-, diaza-, triaza-  
20 , oxadiaz- or tetraaza-aryl radical or a 6-membered aza- or diaza-aryl radical, and as lower alkyl radical, for example, C<sub>1</sub>-C<sub>7</sub> alkyl, preferably C<sub>1</sub>-C<sub>4</sub> alkyl, and is, for example, pyrrolidinyl-lower alkyl, e.g. oxopyrrolidinyl-C<sub>1</sub>-C<sub>4</sub> alkyl, imidazolyl-lower alkyl, e.g. imidazol-4-yl-C<sub>1</sub>-C<sub>4</sub> alkyl,  
25 benzimidazolyl-lower alkyl, e.g. benzimidazol-2-yl-C<sub>1</sub>-C<sub>4</sub> alkyl, oxodiazolyl-lower alkyl, e.g. 1,2,4-oxadiazol-5-yl-C<sub>1</sub>-C<sub>4</sub> alkyl, pyridyl-lower alkyl, e.g. pyridin-2-yl-C<sub>1</sub>-C<sub>4</sub> alkyl, oxopiperidinyl-C<sub>1</sub>-C<sub>4</sub> alkyl, dioxopiperidinyl-C<sub>1</sub>-C<sub>4</sub> alkyl, oxothiazolyl-C<sub>1</sub>-C<sub>4</sub> alkyl, oxo-oxazolinyl-C<sub>1</sub>-C<sub>4</sub> alkyl or  
30 quinolinyl-lower alkyl, e.g. quinolin-2-yl-C<sub>1</sub>-C<sub>4</sub> alkyl, also morpholinocarbonyl-lower alkyl or unsubstituted or N-lower alkanoylated piperidyl-lower alkyl.

Hereinbefore and hereinafter, lower radicals and compounds are to be understood as being, for example, those having up to and including 7, preferably up to and including 4, carbon atoms.

5- or 6-Membered carboxycycloalkyl-lower alkyl, lower  
 5 alkoxy-carbonylcycloalkyl-lower alkyl, carbamoylcycloalkyl-lower  
 alkyl, N-mono- or N,N-di-lower alkylcarbamoylcyclo-alkyl-lower  
 alkyl is, for example, omega (i.e., "ω")-(1-carboxycycloalkyl)-  
 C<sub>1</sub>-C<sub>4</sub> alkyl, ω-(1-lower alkoxy-carbonylcycloalkyl)-C<sub>1</sub>-C<sub>4</sub> alkyl,  
 ω-(1-carbamoylcycloalkyl)-C<sub>1</sub>-C<sub>4</sub> alkyl, ω-(1-lower  
 10 alkylcarbamoylcycloalkyl)-C<sub>1</sub>-C<sub>4</sub> alkyl or ω-(1-di-lower  
 alkylcarbamoylcycloalkyl)-C<sub>1</sub>-C<sub>4</sub> alkyl, wherein cycloalkyl is,  
 for example, cyclopentyl or cyclohexyl, lower alkoxy-carbonyl is,  
 for example, C<sub>1</sub>-C<sub>4</sub> alkoxy-carbonyl, such as methoxy- or  
 ethoxy-carbonyl, lower alkylcarbamoyl is, for example, C<sub>1</sub>-C<sub>4</sub>  
 15 alkylcarbamoyl, such as methylcarbamoyl, di-lower alkylcarbamoyl  
 is, for example, di-C<sub>1</sub>-C<sub>4</sub> alkylcarbamoyl, such as  
 dimethylcarbamoyl, and lower alkyl is, for example, C<sub>1</sub>-C<sub>4</sub> alkyl,  
 such as methyl, ethyl, propyl or butyl, especially (1-  
 carboxycyclopentyl)methyl.

20 5- or 6-Membered cycloalkoxy-lower alkoxy is, for example,  
 cyclopentyloxy- or cyclohexyloxy-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as  
 cyclopentyloxy- or cyclohexyloxy-methoxy, 2-cyclopentyloxy- or  
 2-cyclohexyloxy-ethoxy, 2- or 3-cyclopentyloxy- or 2- or 3-  
 cyclohexyloxy-propyloxy or 4-cyclopentyloxy- or 4-cyclohexyloxy-  
 25 butyloxy, especially cyclopentyloxy- or cyclohexyloxy-methoxy.

5- or 6-Membered cycloalkoxy-lower alkyl is, for example,  
 cyclopentyloxy- or cyclohexyloxy-C<sub>1</sub>-C<sub>4</sub> alkyl, such as  
 cyclopentyloxy- or cyclohexyloxy-methyl, 2-cyclopentyloxy- or 2-  
 cyclohexyloxy-ethyl, 2- or 3-cyclopentyloxy- or 2- or 3-  
 30 cyclohexyloxy-propyl, 2-cyclopentyloxy- or 2-cyclohexyloxy-2-  
 methyl-propyl, 2-cyclopentyloxy- or 2-cyclohexyloxy-2-ethyl-

butyl or 4-cyclopentyloxy- or 4-cyclohexyloxy-butyl, especially cyclopentyloxy- or cyclohexyloxy-methyl.

Amino-lower alkoxy is, for example, amino-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as 2-aminoethoxy or 5-aminopentyloxy, also 3-aminopropyloxy or 4-aminobutyloxy.

Amino-lower alkyl is, for example, amino-C<sub>1</sub>-C<sub>4</sub> alkyl, such as 2-aminoethyl, 3-aminopropyl or 4-aminobutyl.

Carbamoyl-(hydroxy)-lower alkyl is, for example, carbamoyl-C<sub>1</sub>-C<sub>7</sub> (hydroxy)alkyl, such as 1-carbamoyl-2-hydroxyethyl.

Carbamoyl-lower alkoxy is, for example, carbamoyl-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as carbamoylmethoxy, 2-carbamoylethoxy, 3-carbamoylpropyloxy or 4-carbamoylbutyloxy, especially carbamoylmethoxy.

Carbamoyl-lower alkyl is, for example, carbamoyl-C<sub>1</sub>-C<sub>7</sub> alkyl, such as carbamoylmethyl, 2-carbamoylethyl, 3-carbamoylpropyl, 2-(3-carbamoyl)propyl, 2-carbamoylpropyl, 3-(1-carbamoyl)propyl, 2-(2-carbamoyl)propyl, 2-(carbamoyl-2-methyl)propyl, 4-carbamoylbutyl, 1-carbamoylbutyl, 1-(1-carbamoyl-2-methyl)butyl or 3-(4-carbamoyl-2-methyl)butyl.

Carboxy-(hydroxy)-lower alkyl is, for example, carboxy-C<sub>1</sub>-C<sub>7</sub> (hydroxy)alkyl, such as 1-carboxy-2-hydroxy-ethyl.

Carboxy-lower alkoxy is, for example, carboxy-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as carboxymethoxy, 2-carboxyethoxy, 2- or 3-carboxypropyloxy or 4-carboxybutyloxy, especially carboxymethoxy.

Carboxy-lower alkyl is, for example, carboxy-C<sub>1</sub>-C<sub>4</sub> alkyl, such as carboxymethyl, 2-carboxyethyl, 2- or 3-carboxypropyl, 2-carboxy-2-methyl-propyl, 2-carboxy-2-ethyl-butyl or 4-carboxybutyl, especially carboxymethyl.

Cyano-lower alkoxy is, for example, cyano-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as cyanomethoxy, 2-cyano-ethoxy, 2- or 3-cyanopropyloxy or 4-cyanobutyloxy, especially cyanomethoxy.

Cyano-lower alkyl is, for example, cyano-C<sub>1</sub>-C<sub>4</sub> alkyl, such as cyanomethyl, 2-cyanoethyl, 2- or 3-cyanopropyl, 2-cyano-2-methyl-propyl, 2-cyano-2-ethyl-butyl or 4-cyanobutyl, especially cyanomethyl.

5 Di-(N-mono- or N,N-di-lower alkylcarbamoyl)-lower alkyl is, for example, di-(N-mono- or N,N-di-C<sub>1</sub>-C<sub>4</sub> alkylcarbamoyl)-C<sub>1</sub>-C<sub>4</sub> alkyl, such as 1,2-di-(N-mono- or N,N-di-C<sub>1</sub>-C<sub>4</sub> alkylcarbamoyl)ethyl or 1,3-di-(N-mono- or N,N-di-C<sub>1</sub>-C<sub>4</sub> alkylcarbamoyl)propyl.

10 Dicarbamoyl-lower alkyl is, for example, dicarbamoyl-C<sub>1</sub>-C<sub>4</sub> alkyl, such as 1,2-dicarbamoylethyl or 1,3-dicarbamoylpropyl.

Dicarboxy-lower alkyl is, for example, dicarboxy-C<sub>1</sub>-C<sub>4</sub> alkyl, such as 1,2-dicarboxyethyl or 1,3-dicarboxypropyl.

15 Dimethylmorpholino-lower alkoxy can be N-oxidised and is, for example, 2,6-dimethylmorpholino- or 3,5-dimethylmorpholino-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as 2,6-dimethylmorpholino- or 3,5-dimethylmorpholino-methoxy, 2-(2,6-dimethylmorpholino- or 3,5-dimethylmorpholino)-ethoxy, 3-(2,6-dimethylmorpholino- or 3,5-dimethylmorpholino)-propyloxy, 2-(2,6-dimethylmorpholino- or 3,5-dimethylmorpholino-3-methyl)propyloxy, or 1- or 2-[4-(2,6-dimethylmorpholino- or 3,5-dimethylmorpholino)]-butyloxy.

25 Dimethylmorpholino-lower alkyl can be N-oxidised and is, for example, 2,6-dimethylmorpholino- or 3,5-dimethylmorpholino-C<sub>1</sub>-C<sub>4</sub> alkyl, such as 2,6-dimethylmorpholino- or 3,5-dimethylmorpholino-methoxy, 2-(2,6-dimethylmorpholino- or 3,5-dimethylmorpholino)-ethoxy, 3-(2,6-dimethylmorpholino- or 3,5-dimethylmorpholino)-propyl, 2-(2,6-dimethylmorpholino- or 3,5-dimethylmorpholino-3-methyl)-propyl, or 1- or 2-[4-(2,6-dimethylmorpholino- or 3,5-dimethylmorpholino)]-butyl.

30 Di-lower alkoxy-carbonyl-lower alkyl is, for example, di-lower alkoxy-carbonyl-C<sub>1</sub>-C<sub>4</sub> alkyl, such as 1,2-dimethoxycarbonylethyl, 1,3-dimethoxycarbonylpropyl, 1,2-dimethoxycarbonylethyl or 1,3-diethoxycarbonylpropyl.

Di-lower alkylamino is, for example, di-C<sub>1</sub>-C<sub>4</sub> alkylamino, such as dimethylamino, N-methyl-N-ethylamino, diethylamino, N-methyl-N-propylamino or N-butyl-N-methylamino.

Di-lower alkylamino-lower alkoxy is, for example, N,N-di-  
5 C<sub>1</sub>-C<sub>4</sub> alkylamino-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as 2-dimethylaminoethoxy, 3-dimethylaminopropoxy, 4-dimethylaminobutyloxy, 2-diethylaminoethoxy, 2-(N-methyl-N-ethyl-amino)ethoxy or 2-(N-butyl-N-methyl-amino)ethoxy.

Di-lower alkylamino-lower alkyl is, for example, N,N-di-C<sub>1</sub>-  
10 C<sub>4</sub> alkylamino-C<sub>1</sub>-C<sub>4</sub> alkyl, such as 2-dimethylaminoethyl, 3-dimethylaminopropyl, 4-dimethylaminobutyl, 2-diethylaminoethyl, 2-(N-methyl-N-ethyl-amino)ethyl or 2-(N-butyl-N-methyl-amino)ethyl.

Di-lower alkylcarbamoyl-lower alkoxy is, for example, N,N-  
15 di-C<sub>1</sub>-C<sub>4</sub> alkylcarbamoyl-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as methyl- or dimethyl-carbamoyl-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as N-methyl-, N-butyl- or N,N-dimethyl-carbamoylmethoxy, 2-(N-methylcarbamoyl)ethoxy, 2-(N-butylcarbamoyl)ethoxy, 2-(N,N-dimethylcarbamoyl)ethoxy, 3-(N-methylcarbamoyl)propoxy, 3-(N-butylcarbamoyl)propoxy, 3-  
20 (N,N-dimethylcarbamoyl)propoxy or 4-(N-methylcarbamoyl)butyloxy, 4-(N-butylcarbamoyl)butyloxy or 4-(N,N-dimethylcarbamoyl)butyloxy, especially N-methyl-, N-butyl- or N,N-dimethyl-carbamoylmethoxy.

Di-lower alkylcarbamoyl-lower alkyl is, for example, N,N-  
25 di-C<sub>1</sub>-C<sub>4</sub> alkylcarbamoyl-C<sub>1</sub>-C<sub>4</sub> alkyl, such as 2-dimethylcarbamoylethyl, 3-dimethylcarbamoylpropyl, 2-dimethylcarbamoylpropyl, 2-(dimethylcarbamoyl-2-methyl)propyl or 2-(1-dimethylcarbamoyl-3-methyl)butyl.

Di-lower alkylsulfamoyl-lower alkyl is, for example, N,N-  
30 di-C<sub>1</sub>-C<sub>4</sub> alkylsulfamoyl-C<sub>1</sub>-C<sub>4</sub> alkyl, N,N-dimethylsulfamoyl-C<sub>1</sub>-C<sub>4</sub> alkyl, such as N,N-dimethylsulfamoylmethyl, 2-(N,N-dimethylcarbamoyl)ethyl, 3-(N,N-dimethylcarbamoyl)propyl or 4-

(N,N-dimethylcarbamoyl)butyl, especially N,N-dimethylcarbamoylmethyl.

Unsubstituted or N-lower alkanoylated piperidyl-lower alkyl is, for example, 1-C<sub>1</sub>-C<sub>7</sub> -lower alkanoylpiperidin-4-yl-C<sub>1</sub>-C<sub>4</sub> alkyl, such as 1-acetylpiperidinylmethyl or 2-(1-acetylpiperidinyl)ethyl.

Optionally partially hydrogenated or N-oxidised pyridyl-lower alkoxy is, for example, optionally partially hydrogenated pyridyl- or N-oxidopyridyl-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as pyridyl- or N-oxidopyridyl-methoxy, 2-pyridylethoxy, 2- or 3-pyridylpropyloxy or 4-pyridylbutyloxy, especially 3- or 4-pyridylmethoxy.

Optionally partially hydrogenated or N-oxidised pyridyl-lower alkyl is, for example, optionally partially hydrogenated pyridyl- or N-oxidopyridyl-C<sub>1</sub>-C<sub>4</sub> alkyl, such as pyridyl- or N-oxidopyridyl-methyl, 2-pyridylethyl, 2- or 3-pyridylpropyl or 4-pyridylbutyl, especially 3- or 4-pyridylmethyl.

Halo-(hydroxy)-lower alkoxy is, for example, halo-C<sub>2</sub>-C<sub>7</sub> (hydroxy)alkoxy, especially halo-C<sub>2</sub>-C<sub>4</sub> (hydroxy)alkoxy, such as 3-halo-, such as 3-chloro-2-hydroxy-propyloxy.

Hydroxy-lower alkoxy is, for example, hydroxy-C<sub>2</sub>-C<sub>7</sub> alkoxy, especially hydroxy-C<sub>2</sub>-C<sub>4</sub> alkoxy, such as 2-hydroxybutyloxy, 3-hydroxypropyloxy or 4-hydroxybutyloxy.

Hydroxy-lower alkyl is, for example, hydroxy-C<sub>2</sub>-C<sub>7</sub> alkyl, especially hydroxy-C<sub>2</sub>-C<sub>4</sub> alkyl, such as 2-hydroxyethyl, 3-hydroxypropyl or 4-hydroxybutyl.

Hydroxypiperidino-lower alkyl is, for example, 3- or 4-hydroxypiperidino-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as 3- or 4-hydroxypiperidinomethoxy, 2-(3- or 4-hydroxypiperidino)ethoxy, 3-(3- or 4-hydroxypiperidino)propyloxy or 4-(3- or 4-hydroxypiperidino)butyloxy.

Imidazolyl-lower alkyl is, for example, imidazolyl-C<sub>1</sub>-C<sub>4</sub> alkyl, such as imidazol-4-yl-methyl, 2-(imidazol-4-yl)ethyl, 3-(imidazol-4-yl)propyl or 4-(imidazol-4-yl)butyl.

Imidazolyl-lower alkoxy is, for example, imidazolyl-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as imidazol-4-yl-methoxy, 2-(imidazol-4-yl)ethoxy, 3-(imidazol-4-yl)propyloxy or 4-(imidazol-4-yl)butyloxy.

Imidazolyl-lower alkyl is, for example, imidazolyl-C<sub>1</sub>-C<sub>4</sub> alkyl, such as imidazol-4-yl-methyl, 2-(imidazol-4-yl)ethyl, 3-(imidazol-4-yl)propyl or 4-(imidazol-4-yl)butyl.

Morpholinocarbonyl-lower alkyl is, for example, morpholinocarbonyl-C<sub>1</sub>-C<sub>4</sub> alkyl, such as 1-morpholinocarbonylethyl, 3-morpholinocarbonylpropyl, or 1-(morpholinocarbonyl-2-methyl)propyl.

Morpholino-lower alkoxy can be N-oxidised and is, for example, morpholino-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as 1-morpholinoethoxy, 3-morpholinopropyloxy, or 1-(morpholino-2-methyl)propyloxy.

Morpholino-lower alkyl can be N-oxidised and is, for example, morpholino-C<sub>1</sub>-C<sub>4</sub> alkyl, such as morpholinomethyl, 2-morpholinoethyl, 3-morpholinopropyl or 1- or 2-(4-morpholino)butyl.

Lower alkanoyl is, for example, C<sub>1</sub>-C<sub>7</sub> alkanoyl, especially C<sub>2</sub>-C<sub>6</sub> alkanoyl, such as acetyl, propionyl, butyryl, isobutyryl or pivaloyl.

Lower alkanoylamino is, for example, N-C<sub>1</sub>-C<sub>7</sub> alkanoylamino, such as acetylamino or pivaloylamino.

Lower alkanoylamino is, for example, N-C<sub>1</sub>-C<sub>7</sub> alkanoylamino, such as acetylamino or pivaloylamino.

Lower alkanoylamino-lower alkyl is, for example, N-C<sub>1</sub>-C<sub>4</sub> alkanoylamino-C<sub>1</sub>-C<sub>4</sub> alkyl, such as 2-acetoxyaminoethyl.

Lower alkanoylamino-lower alkyl is, for example, N-C<sub>1</sub>-C<sub>4</sub> alkanoylamino-C<sub>1</sub>-C<sub>4</sub> alkyl, such as 2-acetoxyaminoethyl.

Lower alkanoyl-lower alkoxy (oxo-lower alkoxy) carries the lower alkanoyl group in a position higher than the  $\alpha$ -position and is, for example, C<sub>1</sub>-C<sub>7</sub> alkanoyl-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as 4-acetylbutoxy.



Lower alkanoyloxy-lower alkyl carries the lower alkanoyloxy group in a position higher than the  $\alpha$ -position and is, for example, C<sub>1</sub>-C<sub>7</sub> alkanoyloxy-C<sub>1</sub>-C<sub>4</sub> alkyl, such as 4-acetoxy-butyl.

Lower alkanesulfonyl-(hydroxy)-lower alkoxy is, for example, C<sub>1</sub>-C<sub>7</sub> alkanesulfonyl-C<sub>1</sub>-C<sub>4</sub> (hydroxy)alkoxy, such as 3-methanesulfonyl-2-hydroxy-propyloxy.

Lower alkanesulfonyl-lower alkoxy is, for example, C<sub>1</sub>-C<sub>7</sub> alkanesulfonyl-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as methanesulfonylmethoxy or 3-methanesulfonyl-2-hydroxy-propyloxy.

Lower alkanesulfonylamino-lower alkoxy is, for example, C<sub>1</sub>-C<sub>7</sub> alkanesulfonylamino-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as ethanesulfonylaminomethoxy, 2-ethanesulfonylaminoethoxy, 3-ethanesulfonylaminopropyloxy or 3-(1,1-dimethylethanesulfonylamino)propyloxy.

Lower alkanesulfonylamino-lower alkyl is, for example, C<sub>1</sub>-C<sub>7</sub> alkanesulfonylamino-C<sub>1</sub>-C<sub>4</sub> alkyl, such as ethanesulfonylaminomethyl, 2-ethanesulfonylaminoethyl, 3-ethanesulfonylaminopropyl or 3-(1,1-dimethylethanesulfonylamino)propyl.

Lower alkanesulfonyl-lower alkyl is, for example, C<sub>1</sub>-C<sub>7</sub> alkanesulfonyl-C<sub>1</sub>-C<sub>4</sub> alkyl, such as ethanesulfonylmethyl, 2-ethanesulfonylethyl, 3-ethanesulfonylpropyl or 3-(1,1-dimethylethanesulfonyl)propyl.

Lower alkenyl is, for example, C<sub>1</sub>-C<sub>7</sub> alkenyl, such as vinyl or allyl.

Lower alkenyloxy is, for example, C<sub>1</sub>-C<sub>7</sub> alkenyloxy, such as allyloxy.

Lower alkenyloxy-lower alkoxy is, for example, C<sub>1</sub>-C<sub>7</sub> alkenyloxy-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as allyloxymethoxy.

Lower alkenyloxy-lower alkyl is, for example, C<sub>1</sub>-C<sub>7</sub> alkenyloxy-C<sub>1</sub>-C<sub>4</sub> alkyl, such as allyloxymethyl.

Lower alkoxy is, for example, C<sub>1</sub>-C<sub>7</sub> alkoxy, preferably C<sub>1</sub> - C<sub>5</sub> alkoxy, such as methoxy, ethoxy, propyloxy, isopropyloxy,

butyloxy, isobutyloxy, secondary butyloxy, tertiary butyloxy, pentyloxy or a hexyloxy or heptyloxy group.

Lower alkoxy carbonyl is, for example, C<sub>1</sub>-C<sub>7</sub> alkoxy carbonyl, preferably C<sub>1</sub>-C<sub>5</sub> alkoxy carbonyl, such as methoxycarbonyl, 5 ethoxycarbonyl, propyloxycarbonyl, isopropyloxycarbonyl, butyloxycarbonyl, isobutyloxycarbonyl, secondary butyloxycarbonyl, tertiary butyloxy, pentyloxycarbonyl or a hexyloxycarbonyl or heptyloxycarbonyl group.

10 Lower alkoxy carbonyl-(hydroxy)-lower alkyl is, for example, C<sub>1</sub>-C<sub>4</sub> alkoxy carbonyl-C<sub>1</sub>-C<sub>7</sub> (hydroxy)alkyl, such as 1-methoxycarbonyl- or 1-ethoxycarbonyl-2-hydroxy-ethyl.

Lower alkoxy carbonylamino-lower alkoxy is, for example, C<sub>1</sub>-C<sub>7</sub> alkoxy carbonylamino-C<sub>2</sub>-C<sub>7</sub> alkoxy, preferably C<sub>2</sub>-C<sub>5</sub> alkoxy carbonylamino-C<sub>2</sub>-C<sub>7</sub> alkoxy, such as methoxycarbonylamino-15 C<sub>2</sub>-C<sub>7</sub> alkoxy, ethoxycarbonylamino-C<sub>2</sub>-C<sub>7</sub> alkoxy, propyloxycarbonylamino-C<sub>2</sub>-C<sub>7</sub> alkoxy, isobutyloxycarbonylamino-C<sub>2</sub>-C<sub>7</sub> alkoxy, butyloxycarbonylamino-C<sub>2</sub>-C<sub>7</sub> alkoxy, isobutyloxycarbonylamino-C<sub>2</sub>-C<sub>7</sub> alkoxy, secondary butyloxycarbonylamino-C<sub>2</sub>-C<sub>7</sub> alkoxy or tertiary butyloxyamino-C<sub>2</sub>-20 C<sub>7</sub> alkoxy, wherein C<sub>2</sub>-C<sub>7</sub> alkoxy is, for example, methoxy, ethoxy, propyloxy, butyloxy, pentyloxy or hexyloxy.

Lower alkoxy carbonylamino-lower alkyl is, for example, C<sub>1</sub>-C<sub>7</sub> alkoxy carbonylamino-C<sub>2</sub>-C<sub>7</sub> alkyl, preferably C<sub>2</sub>-C<sub>5</sub> alkoxy carbonylamino-C<sub>2</sub>-C<sub>7</sub> alkyl, such as methoxycarbonyl-C<sub>2</sub>-C<sub>7</sub> 25 alkyl, ethoxycarbonylamino-C<sub>2</sub>-C<sub>7</sub> -alkyl, propyloxycarbonylamino-C<sub>2</sub>-C<sub>7</sub>-alkyl isopropyloxycarbonylamino-C<sub>2</sub>-C<sub>7</sub> alkyl, butyloxycarbonylamino-C<sub>2</sub>-C<sub>7</sub> alkyl, isobutyloxycarbonylamino-C<sub>2</sub>-C<sub>7</sub> alkyl, secondary butyloxycarbonylamino-C<sub>2</sub>-C<sub>7</sub> alkyl or tertiary butyloxyamino-C<sub>2</sub>-C<sub>7</sub> alkyl, wherein C<sub>2</sub>-C<sub>7</sub> alkyl is, for example, 30 methyl, ethyl, propyl, butyl, pentyl or hexyl.

Lower alkoxy carbonyl-lower alkoxy is, for example, C<sub>1</sub>-C<sub>4</sub> alkoxy carbonyl-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as methoxycarbonyl- or ethoxycarbonyl-methoxy, 2-methoxycarbonyl- or 2-ethoxycarbonyl-

ethoxy, 2- or 3-methoxycarbonyl- or 2- or 3-ethoxycarbonyl-propyloxy or 4-methoxycarbonyl- or 4-ethoxycarbonyl-butyloxy, especially methoxycarbonyl- or ethoxycarbonyl-methoxy or 3-methoxycarbonyl- or 3-ethoxycarbonyl-propyloxy.

5 Lower alkoxy-carbonyl-lower alkyl is, for example, C<sub>1</sub>-C<sub>4</sub> alkoxy-carbonyl-C<sub>1</sub>-C<sub>4</sub> alkyl, such as methoxycarbonyl- or ethoxycarbonyl-methoxy, 2-methoxycarbonyl- or 2-ethoxycarbonyl-ethoxy, 3-methoxycarbonyl- or 3-ethoxycarbonyl-propyloxy or 4-ethoxycarbonylbutyloxy.

10 Lower alkoxy-lower alkenyl is, for example, C<sub>1</sub>-C<sub>4</sub> alkoxy-C<sub>2</sub>-C<sub>4</sub> alkenyl, such as 4-methoxybut-2-enyl.

Lower alkoxy-lower alkoxy is, for example, C<sub>1</sub>-C<sub>4</sub> alkoxy-C<sub>2</sub>-C<sub>4</sub> alkoxy, such as 2-methoxy-, 2-ethoxy- or 2-propyloxy-ethoxy, 3-methoxy- or 3-ethoxy-propyloxy or 4-methoxybutyloxy, especially 3-methoxypropyloxy or 4-methoxybutyloxy.

15 Lower alkoxy-lower alkoxy-lower alkyl is, for example, C<sub>1</sub>-C<sub>4</sub> alkoxy-C<sub>1</sub>-C<sub>4</sub> alkoxy-C<sub>1</sub>-C<sub>4</sub> alkyl, such as 2-methoxy-, 2-ethoxy- or 2-propyloxy-ethoxymethyl, 2-(2-methoxy-, 2-ethoxy- or 2-propyloxy-ethoxy)ethyl, 3-(3-methoxy- or 3-ethoxy-propyloxy)propyl or 4-(2-methoxybutyloxy)butyl, especially 2-(3-methoxypropyloxy)ethyl or 2-(4-methoxybutyloxy)ethyl.

20 Lower alkoxy-lower alkyl is, for example, C<sub>1</sub>-C<sub>4</sub> alkoxy-C<sub>1</sub>-C<sub>4</sub> alkyl, such as ethoxymethyl, propyloxymethyl, butyloxymethyl, 2-methoxy-, 2-ethoxy- or 2-propyloxy-ethyl, 3-methoxy- or 3-ethoxy-propyl or 4-methoxybutyl, especially 3-methoxypropyl or 4-methoxybutyl.

25 Lower alkoxypiperidino-lower alkyl is, for example, piperidino-, hydroxypiperidino- or lower alkoxypiperidino-C<sub>1</sub>-C<sub>4</sub> alkyl, such as piperidinomethyl, 4-hydroxypiperidinomethyl or 4-C<sub>1</sub>-C<sub>4</sub> alkoxy-, such as 4-methoxy-piperidinomethyl.

30 Lower alkoxypiperidino-lower alkyl is, for example, C<sub>1</sub>-C<sub>4</sub> alkoxypiperidino-C<sub>1</sub>-C<sub>4</sub> alkyl, such as 4-C<sub>1</sub>-C<sub>4</sub> alkoxy-piperidinomethyl, especially 4-methoxypiperidinomethyl.

Lower alkyl may be straight-chained or branched and/or bridged and is, for example, corresponding C<sub>1</sub>-C<sub>7</sub> alkyl, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secondary butyl or tertiary butyl, or a pentyl, hexyl or heptyl group.

5 Lower alkyl R<sub>2</sub> or R<sub>3</sub> is especially C<sub>2</sub>-C<sub>7</sub> alkyl, lower alkyl R<sub>5</sub> or R<sub>7</sub> is especially branched C<sub>3</sub>-C<sub>7</sub> alkyl and lower alkyl R<sub>8</sub> or R<sub>3</sub> is, for example, straight-chained, branched or bridged C<sub>3</sub>-C<sub>7</sub> alkyl.

10 Lower alkylamino is, for example, C<sub>1</sub>-C<sub>4</sub> alkylamino, such as methylamino, ethylamino, propylamino, butylamino, isobutylamino, secondary butylamino or tertiary butylamino.

Lower alkylamino-lower alkoxy is, for example, C<sub>1</sub>-C<sub>4</sub> alkylamino-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as propylaminomethoxy, 2-methylamino-, 2-ethylamino-, 2-propylamino- or 2-butylamino-ethoxy, 3-ethylamino- or 3-propylamino-propyloxy or 4-methylaminobutoxy.

20 Lower alkylamino-lower alkyl is, for example, C<sub>1</sub>-C<sub>4</sub> alkylamino-C<sub>1</sub>-C<sub>4</sub> alkyl, such as propylaminomethyl, 2-methylamino-, 2-ethylamino-, 2-propylamino- or 2-butylamino-ethyl, 3-ethylamino- or 3-propylamino-propyl or 4-methylaminobutyl.

25 Lower alkylcarbamoyl-lower alkoxy is, for example, N-C<sub>1</sub>-C<sub>7</sub> alkylcarbamoyl-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as methyl- or dimethylcarbamoyl-C<sub>1</sub>-C<sub>4</sub> alkoxy, e.g. methylcarbamoylmethoxy, 2-methylcarbamoylethoxy or 3-methylcarbamoylpropyloxy.

Lower alkylenedioxy is, for example, methylenedioxy or ethylenedioxy, but can also be 1,3- or 1,2-propylenedioxy.

30 Lower alkylsulfamoyl-lower alkyl is, for example, N-C<sub>1</sub>-C<sub>7</sub> alkylsulfamoyl-C<sub>1</sub>-C<sub>4</sub> alkyl, such as N-methyl-, N-ethyl-, N-propyl- or N-butyl-sulfamoyl-C<sub>1</sub>-C<sub>4</sub> alkyl, such as N-methyl-, N-ethyl-, N-propyl- or N-butyl-sulfamoylmethyl, 2-(N-methylsulfamoyl)ethyl, 2-(N-butylsulfamoyl)ethyl, 3-(N-methylsulfamoyl)propyl, 3-(N-butylsulfamoyl)propyl, or 4-(N-

methylsulfamoyl)butyl, 4-(N-butylsulfamoyl)butyl or 4-(N,N-dimethylsulfamoyl)butyl, especially N-methyl-, N-butyl- or N,N-dimethyl-sulfamoylmethyl.

Lower alkylthio-(hydroxy)-lower alkoxy is, for example, N-C<sub>1</sub>-C<sub>4</sub> alkylthio-C<sub>1</sub>-C<sub>4</sub> (hydroxy)alkoxy, such as 2-hydroxy-3-methylthiopropoxy.

Oxazolyl-lower alkyl is, for example, oxazolyl-C<sub>1</sub>-C<sub>4</sub> alkyl, such as 2-(1,2,4-oxadiazol-5-yl)ethyl, 3-(1,2,4-oxadiazol-5-yl)propyl or 4-(1,2,4-oxadiazol-5-yl)butyl.

Lower alkylthio-lower alkoxy is, for example, N-C<sub>1</sub>-C<sub>4</sub> alkylthio-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as methylthio-C<sub>1</sub>-C<sub>4</sub> alkoxy, e.g. methylthiomethoxy, 2-methylthioethoxy or 3-methylthiopropoxy.

Lower alkylthio-lower alkyl is, for example, N-C<sub>1</sub>-C<sub>4</sub> alkylthio-C<sub>1</sub>-C<sub>4</sub> alkyl, such as methylthio-C<sub>1</sub>-C<sub>4</sub> alkyl, e.g. methylthiomethyl, 2-methylthioethyl or 3-methylthiopropyl.

N'-Lower alkanoylpiperazino-lower alkoxy is, for example, N'-lower alkanoylpiperazino-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as 4-acetylpiperazinomethoxy.

N'-Lower alkanoylpiperazino-lower alkyl is, for example, N'-C<sub>2</sub>-C<sub>7</sub> -lower alkanoylpiperazino-C<sub>1</sub>-C<sub>4</sub> alkyl, such as 4-acetylpiperazinomethyl.

N'-Lower alkylpiperazino-lower alkyl is, for example, N'-C<sub>1</sub>-C<sub>4</sub> alkylpiperazino-C<sub>1</sub>-C<sub>4</sub> alkyl, such as 4-methylpiperazinomethyl.

Oxo-lower alkoxy is, for example, oxo-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as 3,3-dimethyl-2-oxo-butyloxy.

Piperazino-lower alkyl is, for example, piperazino-C<sub>1</sub>-C<sub>4</sub> alkyl, such as piperazinomethyl, 2-piperazinoethyl or 3-piperazinopropyl.

Piperidino-lower alkoxy is, for example, piperidino-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as piperidinomethoxy, 2-piperidinoethoxy or 3-piperidinopropoxy.

Piperidino-lower alkyl is, for example, piperidino-C<sub>1</sub>-C<sub>4</sub> alkyl, such as piperidinomethyl, 2-piperidinoethyl or 3-piperidinopropyl.

5 Polyhalo-lower alkanesulfonylamino-lower alkoxy is, for example, trifluoro-C<sub>1</sub>-C<sub>7</sub> alkanesulfonyl-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as trifluoromethanesulfonylaminoethyl.

Polyhalo-lower alkanesulfonylamino-lower alkyl is, for example, trifluoro-C<sub>1</sub>-C<sub>7</sub> alkanesulfonyl-C<sub>1</sub>-C<sub>4</sub> alkyl, such as trifluoromethanesulfonylaminoethyl.

10 Pyrimidinyl-lower alkoxy is, for example, pyrimidinyl-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as pyrimidinylmethoxy, 2-pyrimidinylethoxy or 3-pyrimidinylpropyloxy.

Pyrimidinyl-lower alkyl is, for example, pyrimidinyl-C<sub>1</sub>-C<sub>4</sub> alkyl, such as pyrimidinylmethyl, 2-pyrimidinylethyl or 3-pyrimidinylpropyl.

15 Pyrrolidino-lower alkoxy is, for example, pyrrolidino-C<sub>2</sub>-C<sub>4</sub> alkoxy, such as 2-pyrrolidinoethoxy or 3-pyrrolidinopropyloxy.

Pyrrolidino-lower alkyl is, for example, pyrrolidino-C<sub>1</sub>-C<sub>4</sub> alkyl, such as pyrrolidinomethyl, 2-pyrrolidinoethyl or 3-pyrrolidinopropyl.

20 S,S-Dioxothiomorpholino-lower alkyl is, for example, S,S-dioxothiomorpholino-C<sub>1</sub>-C<sub>4</sub> alkyl, such as S,S-dioxothiomorpholinomethyl or 2-(S,S-dioxo)thiomorpholinoethyl.

S-Oxothiomorpholino-lower alkyl is, for example, S-oxothiomorpholino-C<sub>1</sub>-C<sub>4</sub> alkyl, such as S-oxothiomorpholinomethyl or 2-(S-oxo)thiomorpholinoethyl.

Sulfamoyl-lower alkyl is, for example, sulfamoyl-C<sub>1</sub>-C<sub>4</sub> alkyl, such as sulfamoyl-C<sub>1</sub>-C<sub>4</sub> alkyl, such as sulfamoylmethyl, 2-sulfamoylethyl, 3-sulfamoylpropyl or 4-sulfamoylbutyl.

30 Tetrazolyl-lower alkyl is, for example, tetrazolyl-C<sub>1</sub>-C<sub>4</sub> alkyl, such as tetrazol-5-ylmethyl, 2-(tetrazol-5-yl)ethyl, 3-(tetrazol-5-yl)propyl or 4-(tetrazol-4-yl)butyl.

Thiazoliny-lower alkoxy is, for example, thiazoliny-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as thiazolinylmethoxy, 2-thiazolinylmethoxy or 3-thiazolinyloxy.

Thiazoliny-lower alkyl is, for example, thiazoliny-C<sub>1</sub>-C<sub>4</sub> alkyl, such as thiazolinylmethyl, 2-thiazolinyloethyl or 3-thiazolinylopropyl.

Thiazoly-lower alkoxy is, for example, thiazoly-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as thiazolylmethoxy, 2-thiazolyloethyl or 3-thiazolyloxy.

Thiazoly-lower alkyl is, for example, thiazoly-C<sub>1</sub>-C<sub>4</sub> alkyl, such as thiazolylmethyl, 2-thiazolyloethyl or 3-thiazolylopropyl.

Thiomorpholino-lower alkyl or S,S-dioxothiomorpholino-lower alkyl is, for example, thiomorpholino-C<sub>1</sub>-C<sub>4</sub> alkyl, such as -methyl or -ethyl, or S,S-dioxothiomorpholino-C<sub>1</sub>-C<sub>4</sub> alkyl, such as -methyl or -ethyl.

Depending on whether asymmetric carbon atoms are present, the compounds of the invention can be present as mixtures of isomers, especially as racemates, or in the form of pure isomers, especially optical antipodes.

Salts of compounds having salt-forming groups are especially acid addition salts, salts with bases or, where several salt-forming groups are present, can also be mixed salts or internal salts.

Salts are especially the pharmaceutically acceptable or non-toxic salts of compounds of formula 1.

Such salts are formed, for example, by compounds of formula 1 having an acid group, for example a carboxy group or a sulfo group, and are, for example, salts thereof with suitable bases, such as non-toxic metal salts derived from metals of groups Ia, Ib, IIa and IIb of the Periodic Table of the Elements, for example alkali metal salts, especially lithium, sodium or potassium salts, or alkaline earth metal salts, for example

magnesium or calcium salts, also zinc salts or ammonium salts, as well as salts formed with organic amines, such as unsubstituted or hydroxy-substituted mono-, di- or tri-alkylamines, especially mono-, di- or tri-lower alkylamines, or  
5 with quaternary ammonium bases, for example with methyl-, ethyl-, diethyl- or triethyl-amine, mono-, his- or tris-(2-hydroxy-lower alkyl)-amines, such as ethanol-, diethanol- or triethanol-amine, tris-(hydroxymethyl)-methylamine or 2-hydroxy-tert-butylamines, N,N-di-lower alkyl-N-(hydroxy-lower alkyl)-amines,  
10 such as N,N-dimethyl-N-(2-hydroxyethyl)-amine, or N-methyl-D-glucamine, or quaternary ammonium hydroxides, such as tetrabutylammonium hydroxide. The compounds of formula 1 having a basic group, for example an amino group, can form acid addition salts, for example with suitable inorganic acids, for  
15 example hydrohalic acids, such as hydrochloric acid or hydrobromic acid, or sulfuric acid with replacement of one or both protons, phosphoric acid with replacement of one or more protons, e.g. orthophosphoric acid or metaphosphoric acid, or pyrophosphoric acid with replacement of one or more protons, or  
20 with organic carboxylic, sulfonic, sulfo or phosphonic acids or N-substituted sulfamic acids, for example acetic acid, propionic acid, glycolic acid, succinic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, fumaric acid, malic acid, tartaric acid, gluconic acid, glucaric acid, glucuronic acid, citric  
25 acid, benzoic acid, cinnamic acid, mandelic acid, salicylic acid, 4-aminosalicylic acid, 2-phenoxybenzoic acid, 2-acetoxybenzoic acid, embonic acid, nicotinic acid or isonicotinic acid, as well as with amino acids, such as the .alpha.-amino acids mentioned hereinbefore, and with  
30 methanesulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 4-toluenesulfonic acid, naphthalene-2-sulfonic acid, 2- or 3-phosphoglycerate, glucose-6-phosphate, or



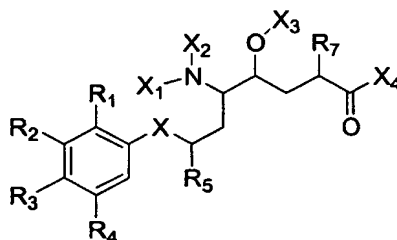
N-cyclohexylsulfamic acid (forming cyclamates) or with other acidic organic compounds, such as ascorbic acid. Compounds of formula 1 having acid and basic groups can also form internal salts.

- 5 For isolation and purification purposes it is also possible to use pharmaceutically unacceptable salts.

The process according to the invention for the preparation of compounds of formula 1 comprises

10

- a) reacting a compound of formula II



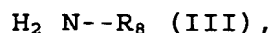
wherein  $X_1$  is lower alkyl, lower alkanoyl or an amino-protecting group,

- 15  $X_2$  is hydrogen or together with  $X_3$  is a bivalent protecting group,

$X_3$  is hydrogen or a hydroxy-protecting group or together with  $X_2$  is a bivalent protecting group or together with  $X_4$  is a direct bond,

- 20  $X_4$  is free or reactively etherified or esterified hydroxy or together with  $X_3$  is a direct bond, and

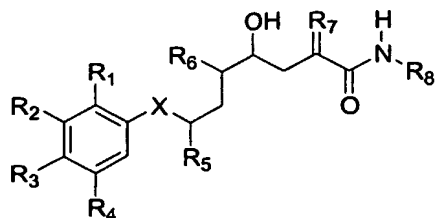
$R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $X$ ,  $R_5$ ,  $R_6$  and  $R_7$  are as defined for formula 1, with an amine of formula III



- 25 wherein

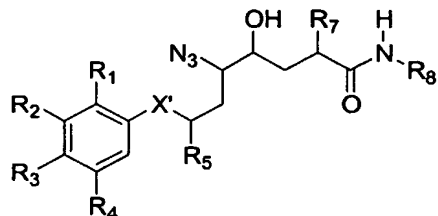
$R_8$  has one of the meanings given for formula 1, with the formation of an amide bond, and removing any protecting groups present, or

b) in a carboxylic acid amide of formula IV



wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $X$ ,  $R_5$ ,  $R_6$ ,  $R_7$  and  $R_8$  are as defined for formula 1 and  $R'_7$  is a lower alkylidene or aryl-lower alkylidene group corresponding to the lower alkyl or aryl-lower alkyl group  $R_7$ , free functional groups being present, if desired, in protected form, or in a salt thereof, reducing the group  $R'_7$  to  $R_7$  by treatment with a hydrogenating agent, or

10 c) for the preparation of compounds of formula 1 wherein  $R_6$  is amino, in a 5-azidocarboxylic acid derivative of formula V



wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_7$  and  $R_8$  are as defined for formula 1,  $X'$  is methylene or free or esterified or etherified

15 hydroxymethyl, and free functional groups are present, if desired, in protected form, or in a salt thereof, reducing the azido group to amino, if desired with the freeing of hydroxymethyl  $X$  or the reduction of  $X'$  to methylene  $X$ , and removing any protecting groups present, and, if desired,

20 converting a compound of formula 1 having at least one salt-forming group obtainable by one of the above-mentioned processes a) to c) into its salt, or converting an obtainable salt into the free compound or into a different salt and/or separating mixtures of isomers that may be obtainable and/or convening a

compound of formula 1 according to the invention into a different compound of formula 1 according to the invention.

Functional groups in starting materials the reaction of which is to be avoided, especially carboxy, amino, hydroxy and mercapto groups, can be protected by suitable protecting groups (conventional protecting groups) which are customarily used in the synthesis of peptide compounds, and also in the synthesis of cephalosporins and penicillins as well as nucleic acid derivatives and sugars. Those protecting groups may already be present in the precursors and are intended to protect the functional groups in question against undesired secondary reactions, such as acylation, etherification, esterification, oxidation, solvolysis, etc.. In certain cases the protecting groups can additionally cause the reactions to proceed selectively, for example stereoselectively. It is characteristic of protecting groups that they can be removed easily, i.e. without undesired secondary reactions taking place, for example by solvolysis, reduction, photolysis, and also enzymatically, for example under physiological conditions. Protecting groups may also be present in the end products, however. Compounds of formula 1 having protected functional groups may have greater metabolic stability or pharmacodynamic properties that are better in some other way than the corresponding compounds having free functional groups.

The protection of functional groups by such protecting groups, the protecting groups themselves and the reactions for their removal are described, for example, in standard works such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in Th. W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York 1981, in "The Peptides", Volume 3 (E. Gross and J. Meienhofer, eds.), Academic Press, London and New York 1981, in "Methoden der organischen Chemie", Houben-Weyl, 4th edition, Volume 15/I,

Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jescheit, "Aminosäuren, Peptide, Proteine" ("Amino acids, peptides, proteins"), Verlag Chemie, Weinheim, Deerfield Beach and Basle 1982, and in Jochen Lehmann, "Chemie der

- 5 Kohlenhydrate: Monosaccharide und Derivate" ("The Chemistry of Carbohydrates: monosaccharides and derivatives"), Georg Thieme Verlag, Stuttgart 1974.

Process variant a) (Formation of the amide bond):

- Amino-protecting groups  $X_1$  are, for example, acyl groups  
10 other than lower alkanoyl, also arylmethyl, lower alkylthio, 2-acyl-lower alk-1-enyl or silyl. The group  $X_1$  -N( $X_2$ )- can also be in the form of an azido group.

- Acyl groups other than lower alkanoyl are, for example, halo-lower alkanoyl, for example 2-haloacetyl, such as 2-chloro-  
15 , 2-bromo-, 2-iodo-, 2,2,2-trifluoro- or 2,2,2-trichloro-acetyl, unsubstituted or substituted, for example halo-, lower alkoxy- or nitro-substituted, benzoyl, for example benzoyl, 4-chlorobenzoyl, 4-methoxybenzoyl or 4-nitrobenzoyl, or lower alkoxy-carbonyl that is branched in the 1-position of the lower  
20 alkyl radical or suitably substituted in the 1- or 2-position, for example tertiary lower alkoxy-carbonyl, such as tert-butoxy-carbonyl, arylmethoxy-carbonyl having one or two aryl radicals which are phenyl that is unsubstituted or mono- or poly-substituted, for example, by lower alkyl, for example  
25 tertiary lower alkyl, such as tertiary butyl, lower alkoxy, such as methoxy, hydroxy, halogen, such as chlorine, and/or by nitro, for example benzyloxy-carbonyl, unsubstituted or substituted benzyloxy-carbonyl, such as 4-nitrobenzyloxy-carbonyl, diphenylmethoxy-carbonyl, fluorenylmethoxy-carbonyl or substituted  
30 diphenylmethoxy-carbonyl, such as di(4-methoxyphenyl)methoxy-carbonyl, aroylmethoxy-carbonyl wherein the aroyl group is preferably benzoyl that is unsubstituted or substituted, for example, by halogen, such as bromine, for

example phenacyloxycarbonyl, 2-halo-lower alkoxycarbonyl, for example 2,2,2-trichloroethoxycarbonyl, 2-bromoethoxycarbonyl or 2-iodo-ethoxycarbonyl, 2-(tri-substituted silyl)-lower alkoxycarbonyl, for example 2-tri-lower alkylsilyl-lower alkoxycarbonyl, for example 2-trimethylsilylethoxycarbonyl or 2-(di-n-butyl-methyl-silyl)-ethoxycarbonyl, or triarylsilyl-lower alkoxycarbonyl, for example 2-triphenylsilylethoxycarbonyl.

In a 2-acyl-lower alk-1-enyl radical that can be used as an amino-protecting group, acyl is, for example, the corresponding radical of a lower alkanecarboxylic acid, of a benzoic acid that is unsubstituted or substituted, for example, by lower alkyl, such as methyl or tertiary butyl, lower alkoxy, such as methoxy, halogen, such as chlorine, and/or by nitro, or especially of a carbonic acid semiester, such as a carbonic acid lower alkyl semiester. Corresponding protecting groups are especially 1-lower alkanoyl-prop-1-en-2-yl, for example 1-acetyl-prop-1-en-2-yl, or lower alkoxycarbonyl-prop-1-en-2-yl, for example 1-ethoxy-carbonyl-prop-1-en-2-yl:

A silylamino group is, for example, a tri-lower alkylsilylamino group, for example trimethylsilylamino. The silicon atom of the silylamino group can also be substituted by only two lower alkyl groups, for example methyl groups, and by the amino group or carboxy group of a second molecule of formula 1. Compounds having such protecting groups can be prepared, for example, using dimethylchlorosilane as silylating agent.

An amino group can also be protected by conversion into the protonated form; suitable corresponding anions are especially those of strong inorganic acids, such as sulfuric acid, phosphoric acid or hydrohalic acids, for example the chlorine or bromine anion, or of organic sulfonic acids, such as p-toluenesulfonic acid.

Preferred amino-protecting groups  $X_1$  are acyl radicals of carbonic acid semiesters, such as lower alkoxycarbonyl,

especially tert-butyloxycarbonyl or fluorenylmethoxycarbonyl, unsubstituted or lower alkyl-, lower alkoxy-, nitro- and/or halo-substituted  $\alpha$ -phenyl- or  $\alpha, \alpha$ -diphenyl-lower alkoxy carbonyl, such as benzyloxycarbonyl, p-nitrobenzyloxy-  
5 carbonyl or diphenylmethoxycarbonyl, or 2-halo-lower alkoxy carbonyl, e.g. 2,2,2-trichloroethoxycarbonyl, also trityl or formyl.

Hydroxy-protecting groups  $X_3$  are, for example, acyl groups, for example lower alkanoyl that is substituted by halogen, such  
10 as chlorine, for example 2,2-dichloroacetyl, or especially acyl radicals of a carbonic acid semiester mentioned for protected amino groups. A preferred hydroxy-protecting group is, for example, 2,2,2-trichloroethoxycarbonyl, 4-nitrobenzyloxycarbonyl, diphenylmethoxycarbonyl or trityl. A  
15 further suitable hydroxy-protecting group  $X_3$  is tri-lower alkylsilyl, for example trimethylsilyl, triisopropylsilyl or dimethyl-tert-butylsilyl, a readily removable etherifying group, for example an alkyl group, such as tertiary lower alkyl, for example tertiary butyl, an oxa- or a thia-aliphatic or -  
20 cycloaliphatic, especially 2-oxa- or 2-thia-aliphatic or -cycloaliphatic, hydrocarbon radical, for example 1-lower alkoxy-lower alkyl or 1-lower alkylthio-lower alkyl, for example methoxymethyl, 1-methoxyethyl, 1-ethoxyethyl, methylthiomethyl, 1-methylthioethyl or 1-ethylthioethyl, or 2-oxa- or 2-thia-  
25 cycloalkyl having from 5 to 7 ring atoms, for example 2-tetrahydrofuryl or 2-tetrahydropyranyl, or a corresponding thia analogue, and also 1-phenyl-lower alkyl, for example benzyl, diphenylmethyl or trityl, wherein the phenyl radicals can be substituted, for example, by halogen, for example chlorine,  
30 lower alkoxy, for example methoxy, and/or by nitro.

Bivalent protecting groups formed by  $X_2$  and  $X_3$  together are, for example, methylene groups substituted by one or two alkyl radicals and are accordingly unsubstituted or substituted

alkylidene, such as lower alkylidene, for example isopropylidene, cycloalkylidene, such as cyclohexylidene, also carbonyl or benzylidene.

If  $X_4$  is reactively etherified or esterified hydroxy, the  
5 terminal group  $--(=O)--X_4$  is a reactively functionally modified carboxylic acid function and is, for example, in the form of an activated ester or anhydride. The reactive acid derivatives can also be formed in situ.

Such activated esters of compounds of formula II are  
10 especially esters unsaturated at the linking carbon atom of the esterifying radical, for example of the vinyl ester type, such as vinyl esters (obtainable, for example, by transesterification of a corresponding ester with vinyl acetate; activated vinyl ester method), carbamoyl esters (obtainable, for example, by  
15 treatment of the corresponding acid with an isoxazolium reagent; 1,2-oxazolium or Woodward method), or 1-lower alkoxyvinyl esters (obtainable, for example, by treatment of the corresponding acid with a lower alkoxyacetylene; ethoxyacetylene method), or esters of the amidino type, such as  $N,N'$ -disubstituted amidino esters  
20 (obtainable, for example, by treatment of the corresponding acid with a suitable  $N,N'$ -disubstituted carbodiimide, for example  $N,N'$ -dicyclohexylcarbodiimide; carbodiimide method), or  $N,N'$ -disubstituted amidino esters (obtainable, for example, by treatment of the corresponding acid with an  $N,N'$ -disubstituted  
25 cyanamide; cyanamide method), suitable aryl esters, especially phenyl esters suitably substituted by electron-attracting substituents (obtainable, for example, by treatment of the corresponding acid with a suitably substituted phenol, for example 4-nitrophenol, 4-methylsulfonylphenol, 2,4,5-  
30 trichlorophenol, 2,3,4,5,6-pentachlorophenol or 4-phenyldiazophenol, in the presence of a condensation agent, such as  $N,N'$ -dicyclohexylcarbodiimide; activated aryl esters method), cyanomethyl esters (obtainable, for example, by treatment of the

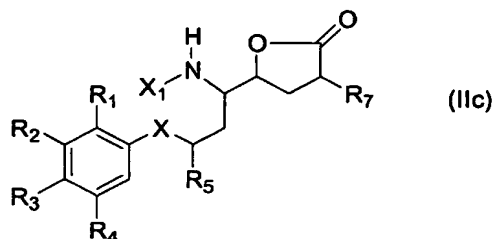
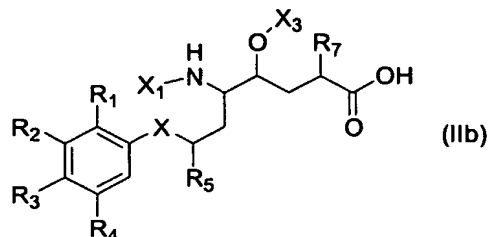
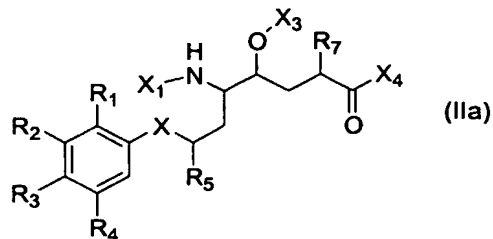
corresponding acid with chloroacetonitrile in the presence of a base; cyanomethyl esters method), thioesters, especially unsubstituted or substituted, for example nitro-substituted, phenylthio esters (obtainable, for example, by treatment of the corresponding acid with unsubstituted or substituted, for example nitro-substituted, thiophenols, inter alia by the anhydride or carbodiimide method; activated thiol esters method), or especially amino or amido esters (obtainable, for example, by treatment of the corresponding acid with an N-hydroxyamino or N-hydroxyamido compound, for example N-hydroxysuccinimide, N-hydroxypiperidine, N-hydroxyphthalimide, N-hydroxy-5-norbornene-2,3-dicarboxylic acid imide, 1-hydroxybenzotriazole or 3-hydroxy-3,4-dihydro-1,2,3-benzotriazin-4-one, for example by the anhydride or carbodiimide method; activated N-hydroxy esters method). Internal esters, for example  $\gamma$ -lactones, can also be used.

Anhydrides of acids of formula II may be symmetric or preferably mixed anhydrides of those acids, for example anhydrides with inorganic acids, such as acid halides, especially acid chlorides (obtainable, for example, by treatment of the corresponding acid with thionyl chloride, phosphorus pentachloride or oxalyl chloride; acid chloride method), azides (obtainable, for example, from a corresponding acid ester via the corresponding hydrazide and treatment thereof with nitrous acid; azide method), anhydrides with carbonic acid semiesters, for example carbonic acid lower alkyl semiesters (obtainable, for example, by treatment of the corresponding acid with chloroformic acid lower alkyl esters or with a 1-lower alkoxy-carbonyl-2-lower alkoxy-1,2-dihydroquinoline; mixed O-alkyl-carbonic acid anhydrides method), or anhydrides with dihalogenated, especially dichlorinated, phosphoric acid (obtainable, for example, by treatment of the corresponding acid with phosphorus oxychloride; phosphorus oxychloride method),



anhydrides with other phosphoric acid derivatives (for example those obtainable with phenyl-N-phenylphosphoramidochloridate) or with phosphorous acid derivatives, or anhydrides with organic acids, such as mixed anhydrides with organic carboxylic acids (obtainable, for example, by treatment of the corresponding acid with an unsubstituted or substituted lower alkane- or phenyl-lower alkane-carboxylic acid halide, for example phenylacetic acid chloride, pivalic acid chloride or trifluoroacetic acid chloride; mixed carboxylic acid anhydrides method) or with organic sulfonic acids (obtainable, for example, by treatment of a salt, such as an alkali metal salt, of the corresponding acid with a suitable organic sulfonic acid halide, such as a lower alkane- or aryl-, for example methane- or p-toluene-sulfonic acid chloride; mixed sulfonic acid anhydrides method) and symmetric anhydrides (obtainable, for example, by condensation of the corresponding acid in the presence of a carbodiimide or 1-diethylaminopropyne; symmetric anhydrides method).

Preferred starting materials of formula II are compounds of formulae IIa, IIb and IIc



wherein  $X_1$  is an amino-protecting group, especially tert-butyloxycarbonyl,

$X_2$  together with  $X_3$  is a bivalent protecting group, especially lower alkylidene, such as isopropylidene, and

$X_3$  in formula IIa is hydrogen or tri-lower alkylsilyl, especially tert-butyl(dimethyl)silyl, or in formula IIb, together with  $X_2$ , is a bivalent protecting group, especially lower alkylidene, such as isopropylidene, and

$X_4$  is hydroxy, lower alkoxy or halogen, such as chlorine.

As mentioned, derivatives of carboxylic acids that are used as acylating agents may also be formed in situ. For example, N,N'-disubstituted amidino esters may be formed in situ by reacting a mixture of the acid used as acylating agent and the starting material of formula III in the presence of a suitable N,N'-disubstituted carbodiimide, for example N,N'-cyclohexylcarbodiimide. In addition, amino or amido esters of the acids used as acylating agents may be formed in the presence

of the starting material of formula III to be acylated, by reacting a mixture of the corresponding acid and amino starting materials in the presence of an N,N'-disubstituted carbodiimide, for example N,N'-dicyclohexylcarbodiimide, and of an N-

5 hydroxyamine or N-hydroxyamide, for example N-hydroxysuccinimide, where appropriate in the presence of a suitable base, for example 4-dimethylamino-pyridine.

The condensation to form an amide bond can be carried out in a manner known per se, for example as described in standard  
10 works, such as Houben-Weyl, "Methoden der organischen Chemie", 4th edition, Volume 15/II (1974), Volume IX (1955), Volume E 11 (1985), Georg Thieme Verlag, Stuttgart, "The Peptides" (E. Gross and J. Meienhofer, eds.), Volumes 1 and 2, Academic Press, London and New York, 1979/1980, or M. Bodansky, "Principles of  
15 Peptide Synthesis", Springer-Verlag, Berlin 1984.

The condensation of a free carboxylic acid with the corresponding amine can be carried out preferably in the presence of one of the customary condensation agents. Customary condensation agents are, for example, carbodiimides, for example  
20 diethyl-, dipropyl-, N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide or especially dicyclohexylcarbodiimide, also suitable carbonyl compounds, for example carbonyldiimidazole, 1,2-oxazolium compounds, for example 2-ethyl-5-phenyl-1,2-oxazolium-3'-sulfonate and 2-tert-butyl-5-methylisoxazolium  
25 perchlorate, or a suitable acylamino compound, for example 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, also activated phosphoric acid derivatives, for example diphenylphosphoryl azide, diethylphosphoryl cyanide, phenyl-N-phenylphosphoromidochloridate, bis(2-oxo-3-  
30 oxazolidinyl)phosphinic acid chloride or 1-benzotriazolyloxy-tris(dimethylamino)phosphonium hexafluorophosphate.

If desired, an organic base may be added, for example a tri-lower alkylamine having bulky radicals, for example

ethyldiisopropylamine, and/or a heterocyclic base, for example pyridine, N-methylmorpholine or preferably 4-dimethylaminopyridine.

The condensation of activated esters, reactive anhydrides  
5 or reactive cyclic amides with the corresponding amines is customarily carried out in the presence of an organic base, for example simple tri-lower alkylamines, for example triethylamine or tributylamine, or one of the above-mentioned organic bases. If desired, a condensation agent may additionally be used, for  
10 example as described for free carboxylic acids.

The condensation of acid anhydrides with amines can be effected, for example, in the presence of inorganic carbonates, for example ammonium or alkali metal carbonates or hydrogen carbonates, such as sodium or potassium carbonate or hydrogen  
15 carbonate (usually together with a sulfate).

Carboxylic acid chlorides, for example the chlorocarbonic acid derivatives derived from the acid of formula II, are condensed with the corresponding amines preferably in the presence of an organic amine, for example the above-mentioned  
20 tri-lower alkylamines or heterocyclic bases, where appropriate in the presence of a hydrogen sulfate.

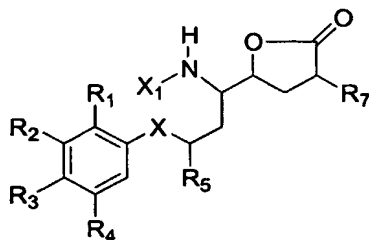
The condensation is preferably carried out in an inert, aprotic, preferably anhydrous, solvent or solvent mixture, for example in a carboxylic acid amide, for example formamide or  
25 dimethylformamide, a halogenated hydrocarbon, for example methylene chloride, carbon tetrachloride or chlorobenzene, a ketone, for example acetone, a cyclic ether, for example tetrahydrofuran, an ester, for example ethyl acetate, or a nitrile, for example acetonitrile, or in a mixture thereof, as  
30 appropriate at reduced or elevated temperature, for example in a temperature range of from approximately -40°C to approximately +100°C, preferably from approximately -10°C to approximately +50°C, and in the case where arylsulfonyl esters are used also

at approximately from +100°C to +200°C, and without an inert gas or under an inert gas atmosphere, for example a nitrogen or argon atmosphere.

Aqueous, for example alcoholic, solvents, for example ethanol, or aromatic solvents, for example benzene or toluene, may also be used. When alkali metal hydroxides are present as bases, acetone can also be added where appropriate.

The condensation can also be carried out in accordance with the technique known as solid-phase synthesis which originates from R. Merrifield and is described, for example, in Angew. Chem. 97, 801-812 (1985), Naturwissenschaften 71, 252-258 (1984) or in R. A. Houghten, Proc. Natl. Acad. Sci. U.S.A. 82, 5131-5135 (1985).

A preferred variant of that process is carried out by reacting, as the activated ester, an internal ester ( $\gamma$ -lactone) derived from the carboxylic acid of formula 1 and having the formula IIc

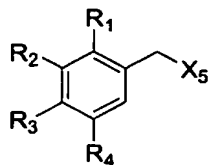


wherein X is methylene, with the compound of formula III, free functional groups present in the reactants, with the exception of the groups participating in the reaction, being if desired, as stated above, in protected form and any protecting groups being removed as described above. The opening of the lactone ring with the formation of the amide bond is carried out under the conditions described above, optionally in the presence of a suitable catalyst. In particular, a  $\gamma$ -lactone IIc may be reacted with a primary amine III without a solvent or in the presence of a polar solvent, for example a lower alcohol, such

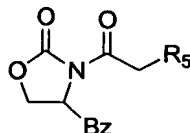
as methanol or ethanol, a polar ether, such as tetrahydrofuran or dioxane, a nitrile, such as acetonitrile, an amide, such as dimethylformamide, N,N-dimethylacetamide, N-methyl-pyrrolidone or hexamethylphosphoric acid triamide, a urea, for example N,N'-  
5 dimethyl-N,N'-propylenylurea, a lower alkoxy-lower alkanol, for example diethylene glycol mono-methyl ether, in dimethyl sulfoxide or in a mixture of the mentioned solvents or in a mixture of one or more of the mentioned solvents with water, at temperatures of from room temperature to 150°C, preferably  
10 approximately from 20°C to 100°C, and in the presence of a catalyst, such as 2-hydroxypyridine and/or triethylamine, the comments made above applying in respect of the protecting groups.

In another preferred variant of that process the starting  
15 material used is a compound of formula IIb wherein X is methylene, which is reacted with the reactant of formula III in the presence of a cyanophosphonic acid diester, for example cyanophosphonic acid diethyl ester, and a tertiary organic amine, such as a tri-lower alkylamine, for example trimethyl-  
20 amine, and in a polar solvent, for example a nitrile, such as acetonitrile, an amide, such as dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone or hexamethyl-phosphoric acid triamide, a urea, for example N,N'-dimethyl-N,N'-propylenylurea, a lower alkoxy-lower alkanol, for example  
25 diethylene glycol monomethyl ether, in dimethyl sulfoxide or in a mixture of the mentioned solvents or in a mixture of one or more of the mentioned solvents with water, at temperatures of from -30°C to 100°C, preferably from 20°C to 80°C, the comments made above applying in respect of the protecting groups.

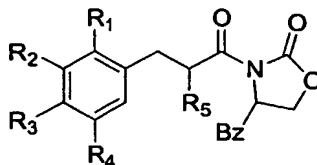
30 Starting materials of formula II can be prepared, for example, by reacting a compound of formula VI



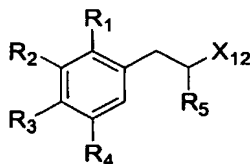
wherein X<sub>5</sub> is free or reactively esterified hydroxy, especially halogen, such as bromine, with a compound of formula VII



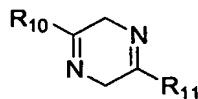
in the resulting compound of formula VIII



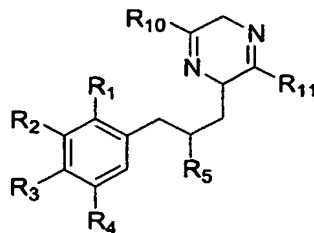
hydrolysing the 4-benzyl-2-oxo-oxazolidin-1-ylcarbonyl group selectively to carboxy, for example by means of lithium hydroxide/hydrogen peroxide; reducing the carboxy group to hydroxymethyl, for example by means of sodium borohydride/iodine in tetrahydrofuran; halogenating the hydroxymethyl group, for example with N-bromosuccinimide/triphenyl-phosphine in dichloromethane, and reacting the reaction product of formula IX



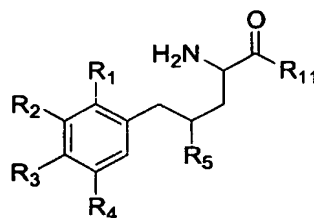
wherein X<sub>12</sub> is halomethyl, with a compound of formula X



wherein R<sub>10</sub> and R<sub>11</sub> are identical or different lower alkoxy groups; hydrolysing the resulting compound of formula XI

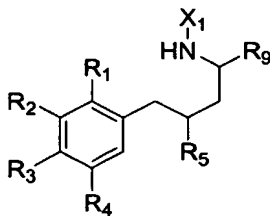


wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are as defined above and R<sub>10</sub> and R<sub>11</sub> are identical or different lower alkoxy groups; protecting the resulting compound of formula XII

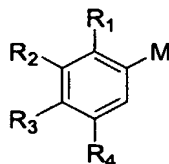


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at the amino group by an amino-protecting group X<sub>1</sub> and, if desired, reacting the resulting compound of formula XIII



wherein R<sub>9</sub> is formyl, with a compound of formula XIV

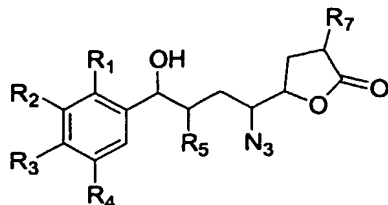


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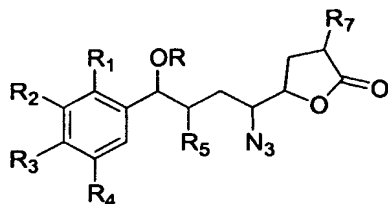
wherein M is a metallic, especially an alkaline earth metallic, radical, for example a group of the formula Mg-Hal (Hal=halogen, especially bromine), in customary manner, for example in an ethereal solvent, such as tetrahydrofuran, with cooling, for example in a temperature range of approximately from -80° to 0°; if desired temporarily protecting the resulting compound of formula XV

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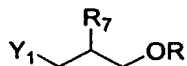
at the hydroxy group, for example by reaction with a lower alkanolic acid anhydride, especially isobutyric acid anhydride, in the presence of dimethylaminopyridine in dichloromethane; in  
 5 the resulting compound of formula XVI



wherein R is hydrogen or a hydroxy-protecting group, such as especially isobutyryl, reducing the azido group to amino, for example by catalytic hydrogenation using palladium-on-carbon, it  
 10 being possible, if desired, for the group --OR to be replaced reductively by hydrogen, and optionally introducing the protecting group X<sub>1</sub>.

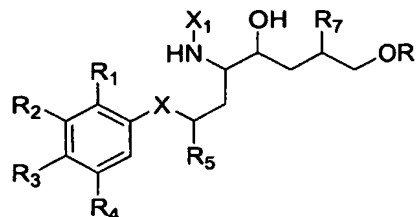
For the preparation of compounds of formula IIa, a compound of formula IIc can be hydrolysed in customary manner with the  
 15 lactone ring being opened, for example by treatment with lithium hydroxide in a water-containing solvent, for example in DME/water, optionally the hydroxy-protecting group X<sub>3</sub> can be introduced and, if desired, the terminal carboxy group can be reactively modified.

20 Starting materials of formula IIb are obtained, for example, by reacting a compound of formula XIII wherein R<sub>9</sub> is formyl with a compound of formula XVII

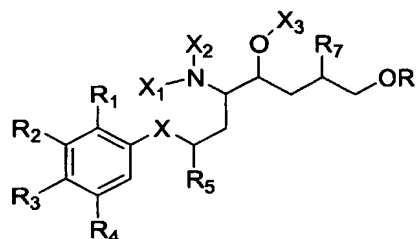


wherein Y<sub>1</sub> is a metallic, especially an alkaline earth  
 25 metallic, radical, for example of the formula --MgHal wherein

Hal is bromine, chlorine or iodine, and OR is etherified hydroxy, such as unsubstituted or substituted benzyloxy, to form the corresponding compound of formula XVIII



- 5 protecting that compound at the amino and hydroxy groups, for example by a bivalent protecting group --X<sub>2</sub> --X<sub>3</sub> --, such as lower alkylidene, especially isopropylidene; in the compound of formula XIX thus protected



- 10 freeing the terminal hydroxy group reductively and converting the terminal hydroxy-methyl group into formyl, for example by treatment with N-methylmorpholine-N-oxide and tetrabutylammonium perruthenate in chloroform, and oxidising the resulting aldehyde to the acid in customary manner, for example  
 15 by treatment with potassium permanganate, or oxidising the resulting terminal alcohol directly to the acid by suitable measures, for example by treatment with sodium iodate/ruthenium chloride, and in each case, if desired, reactively modifying the carboxy function.

- 20 Process variant b) (Reduction of lower alkylidene or aryl-lower alkylidene R'<sub>7</sub> to lower alkyl or aryl-lower alkyl R<sub>7</sub>).

In a starting material of formula IV, functional groups that are not to participate in the reaction are protected by suitable protecting groups mentioned under a).

Hydrogenation agents suitable for the hydrogenation of the olefinic double bond are those which under the reaction conditions of the process reduce the double bond selectively or more rapidly than the amide bonds present in compounds of

5 formula IV.

Especially suitable are hydrogenation agents such as hydrogen in the presence of suitable catalysts.

Catalysts suitable for hydrogenation are metals, for example nickel, iron, cobalt or ruthenium, or noble metals or  
10 their oxides, such as palladium or rhodium or their oxides, optionally supported on a suitable carrier, such as barium sulfate, aluminium oxide or active carbon, or in the form of skeleton catalysts, for example Raney nickel, but especially homogeneous or heterogeneous metal- or noble metal-ligand  
15 complexes, more especially those which produce the configuration at the carbon atom carrying the group  $R_4$  desired in each particular case.

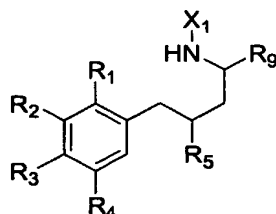
Such catalysts are especially complexes of ruthenium or ruthenium salts, such as Ru(II) halides, such as  $RuCl_2$ ,  $Ru_2Cl_2$   
20 or  $RuHCl$ , optionally halogenated Ru(II) lower alkanoylates, such as  $Ru(OAc)_2$  or  $Ru(OOC-CF_3)_2$ , with (S)-bis(2,2'-diphenylphosphino)-1,1'-bi-naphthyl (S-BINAP) or derivatives thereof which contain instead of phenyl substituted phenyl radicals, such as p-tolyl or p-methoxyphenyl, and also ruthenium  
25 complexes with (S)-bis(2,2'-diphenylphosphino)-5,5'-dimethyldiphenyl and the like. Hydrogenation with complexes of that type is preferably carried out in alcohols, such as lower alkanols, or alkyl halides, such as methylene chloride, in a pressure range of approximately from 1 to 100 bar, preferably from 20 to  
30 30 bar, and in a temperature range of approximately from 10° to 80°C., preferably from 15° to 25°C.

Other solvents customarily used for catalytic hydrogenation are polar organic or inorganic solvents, for example water,

alcohols, esters, dioxane, glacial acetic acid or mixtures of those solvents. The hydrogenation is carried out at temperatures of from 0°C. to 250°C., preferably from room temperature to about 100°C. and at hydrogen pressures of from 1 to 200 bar.

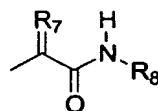
- 5 Hydrogenation methods will be found, for example, in "Organikum, organisch-chemisches Grundpraktikum", 17th revised edition, VEB Deutscher Verlag der Wissenschaften, Berlin 1988.

Carboxylic acid amides of formula 1V are obtained, for example, by condensing an aldehyde of formula XIII



10

wherein R<sub>9</sub> is formyl, in customary manner with a suitable metallated amide compound, for example obtainable by reaction of a compound of formula XX



15

with butyllithium and chlorotitanium triisopropyl oxide.

Process variant c) (Reduction of the azido group):

In starting materials of formula V, functional groups that are not to participate in the reaction are protected by one of the protecting groups mentioned under Process a).

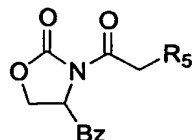
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Reducing agents suitable for the reduction of the azido group are those which under the reaction conditions of the process reduce an optionally functionalised hydroxy group or azido group selectively or more rapidly than the amide groups present in compounds of formula 1.

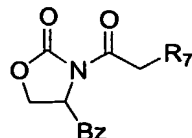
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The reduction is preferably carried out with hydrogen in the presence of suitable heavy metal catalysts, for example Raney nickel or platinum or palladium catalysts, for example platinum or palladium on active carbon.

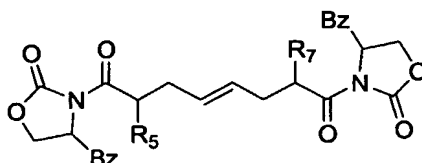
Intermediates of formula V can be prepared, for example, by reacting E-1,4-dibromobut-2-ene first with a compound of formula VII



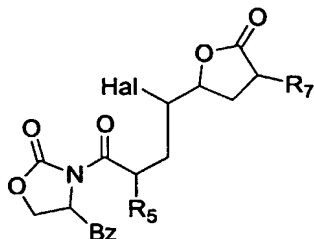
5 and then with a compound of formula XXI



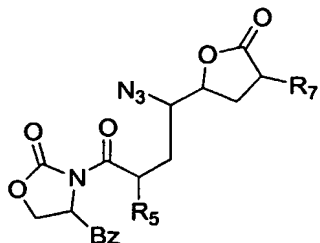
to form the corresponding compound of formula XXII



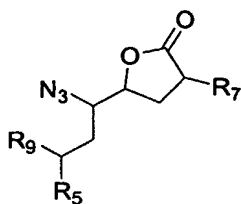
10 converting that compound, for example by treatment with a customary halogenating agent, such as elemental halogen, especially bromine or iodine, or preferably with an N-halosuccinimide, especially N-bromosuccinimide, in 1,2-dimethoxyethane (DME), into the corresponding compound of formula XXIII



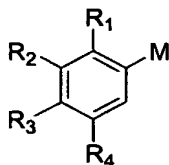
15 wherein Hal is halogen; separating the desired isomer in respect of R5 and R7 and in that isomer replacing the halogen atom by azido, for example by treatment with tetrabenzylammonium azide in toluene, and in the resulting compound of  
20 formula XXIV



wherein R<sub>5</sub> and R<sub>7</sub> are as defined above and Bz is benzyl, hydrolysing the 4-benzyl-2-oxo-oxazolidin-1-ylcarbonyl group selectively to carboxy, for example by treatment with an alkali metal hydroxide in the presence of a basic hydrolysing agent, especially lithium hydroxide in the presence of hydrogen peroxide; re-closing, using an acid catalyst, a lactone ring which may have been opened; in the resulting compound of formula XXV

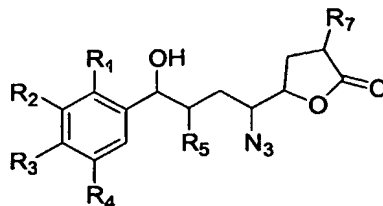


wherein R<sub>9</sub> is carboxy, converting the carboxy group into formyl, for example by conversion into the acid chloride by means of oxalyl chloride and subsequent reduction of the chlorocarbonyl group, for example with sodium tri-tert-butyloxyaluminium hydride in tetrahydrofuran; reacting the resulting compound of formula XXV wherein R<sub>9</sub> is then formyl with a compound of formula XIV

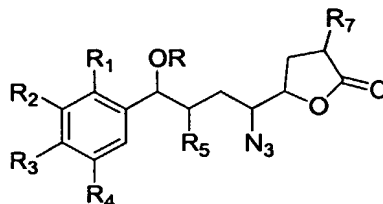


wherein M is a metallic, especially an alkaline earth metallic, radical, for example a group of the formula Mg-Hal (Hal=halogen, especially bromine), in customary manner, for example in an ethereal solvent, such as tetrahydrofuran, with

cooling, for example in a temperature range of approximately from  $-80^{\circ}$  to  $0^{\circ}\text{C}$ ; if desired etherifying or, especially, esterifying the resulting compound of formula XV

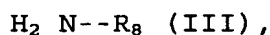


- 5 at the hydroxy group, for example temporarily protecting the hydroxy group by reaction with a lower alkanolic acid anhydride, especially isobutyric acid anhydride, in the presence of dimethylaminopyridine in dichloromethane; reacting the resulting compound of formula XVI



10

wherein the group --OR is a free or esterified or etherified hydroxy group, with R preferably being a hydroxy-protecting group, such as especially isobutyryl, in customary manner, for example as indicated under Process variant a), with an amine of formula III



wherein  $\text{R}_8$  has one of the meanings given under formula 1, and, if desired, freeing hydroxymethyl from the group --OR or replacing the group --OR reductively by hydrogen.

20

The removal of protecting groups that are not constituents of the desired end product of formula 1, for example carboxy-, amino-, hydroxy- and/or mercapto-protecting groups, which may be carried out subsequent to the process variants described above, is effected in a manner known per se, for example by means of solvolysis, especially hydrolysis, alcoholysis or acidolysis, or by means of reduction, especially hydrogenolysis or chemical

25

reduction, as well as photolysis, as appropriate stepwise or simultaneously, it being possible also to use enzymatic methods. The removal of the protecting groups is described, for example, in the standard works mentioned hereinabove in the section

5 relating to protecting groups.

For example, protected carboxy, for example tertiary lower alkoxy-carbonyl, lower alkoxy-carbonyl substituted in the 2-position by a trisubstituted silyl group or in the 1-position by lower alkoxy or by lower alkylthio, or unsubstituted or

10 substituted diphenylmethoxycarbonyl can be converted into free carboxy by treatment with a suitable acid, such as formic acid or trifluoroacetic acid, where appropriate with the addition of a nucleophilic compound, such as phenol or anisole.

Unsubstituted or substituted benzyloxycarbonyl can be freed, for

15 example, by means of hydrogenolysis, i.e. by treatment with hydrogen in the presence of a metal hydrogenation catalyst, such as a palladium catalyst. In addition, suitably substituted benzyloxycarbonyl, such as 4-nitrobenzyloxycarbonyl, can be converted into free carboxy also by reduction, for example by

20 treatment with an alkali metal dithionite, such as sodium dithionite, or with a reducing metal, for example zinc, or a reducing metal salt, such as a chromium(H) salt, for example chromium(II) chloride, customarily in the presence of a hydrogen-yielding agent that, together with the metal, is

25 capable of producing nascent hydrogen, such as an acid, especially a suitable carboxylic acid, such as an unsubstituted or substituted, for example hydroxy-substituted, lower

alkanecarboxylic acid, for example acetic acid, formic acid, glycolic acid, diphenylglycolic acid, lactic acid, mandelic

30 acid, 4-chloromandelic acid or tartaric acid, or in the presence of an alcohol or thiol, water preferably being added. By treatment with a reducing metal or metal salt, as described above, 2-halo-lower alkoxy-carbonyl (where appropriate after



conversion of a 2-bromo-lower alkoxy carbonyl group into a corresponding 2-iodo-lower alkoxy carbonyl group) or aroyl methoxy carbonyl can also be converted into free carboxy. Aroyl methoxy carbonyl can be cleaved also by treatment with a nucleophilic, preferably salt-forming, reagent, such as sodium thiophenolate or sodium iodide. 2-(Tri-substituted silyl)-lower alkoxy carbonyl, such as 2-tri-lower alkylsilyl-lower alkoxy carbonyl, can be converted into free carboxy also by treatment with a salt of hydrofluoric acid that yields the fluoride anion, such as an alkali metal fluoride, for example sodium or potassium fluoride, where appropriate in the presence of a macrocyclic polyether ("crown ether"), or with a fluoride of an organic quaternary base, such as tetra-lower alkyl-ammonium fluoride or tri-lower alkylarylammonium fluoride, for example tetraethylammonium fluoride or tetrabutylammonium fluoride, in the presence of an aprotic, polar solvent, such as dimethyl sulfoxide or N,N-dimethylacetamide. Carboxy protected in the form of organic silyloxy carbonyl, such as tri-lower alkylsilyloxy carbonyl, for example trimethylsilyloxy carbonyl, can be freed in customary manner by solvolysis, for example by treatment with water, an alcohol or an acid, or, furthermore, a fluoride, as described above. Esterified carboxy can also be freed enzymatically, for example by means of esterases or suitable peptidases.

A protected amino group is freed in a manner known per se and, according to the nature of the protecting groups, in various ways, preferably by solvolysis or reduction. 2-Halo-lower alkoxy carbonylamino (where appropriate after conversion of a 2-bromo-lower alkoxy carbonylamino group into a 2-iodo-lower alkoxy carbonylamino group), aroyl methoxy carbonylamino or 4-nitrobenzyloxy carbonylamino can be cleaved, for example, by treatment with a suitable reducing agent, such as zinc in the presence of a suitable carboxylic acid, such as aqueous acetic

acid. Aroylmethoxycarbonylamino can be cleaved also by treatment with a nucleophilic, preferably salt-forming, reagent, such as sodium thiophenolate, and 4-nitrobenzyloxycarbonylamino also by treatment with an alkali metal dithionite, for example sodium

5 dithionite. Unsubstituted or substituted diphenylmethoxycarbonylamino, tert-lower alkoxy carbonylamino or 2-(tri-substituted silyl)-lower alkoxy carbonylamino, such as 2-tri-lower alkylsilyl-lower alkoxy carbonylamino, can be cleaved by treatment with a suitable acid, for example formic or

10 trifluoroacetic acid; unsubstituted or substituted benzyloxycarbonylamino can be cleaved, for example, by means of hydrogenolysis, i.e. by treatment with hydrogen in the presence of a suitable hydrogenation catalyst, such as a palladium catalyst; unsubstituted or substituted triarylmethylamino or

15 formylamino can be cleaved, for example, by treatment with an acid, such as a mineral acid, for example hydrochloric acid, or an organic acid, for example formic, acetic or trifluoroacetic acid, where appropriate in the presence of water; and an amino group protected in the form of silylamino can be freed, for

20 example, by means of hydrolysis or alcoholysis. An amino group protected by 2-haloacetyl, for example 2-chloroacetyl, can be freed by treatment with thiourea in the presence of a base, or with a thiolate salt, such as an alkali metal thiolate of thiourea, and subsequent solvolysis, such as alcoholysis or

25 hydrolysis, of the resulting condensation product. An amino group protected by 2-(tri-substituted silyl)-lower alkoxy carbonyl, such as 2-tri-lower alkylsilyl-lower alkoxy carbonyl, can be converted into the free amino group also by treatment with a salt of hydrofluoric acid that yields

30 fluoride anions, as indicated above in connection with the freeing of a correspondingly protected carboxy group. Likewise, silyl, such as trimethylsilyl, bonded directly to a hetero atom, such as nitrogen, can be removed using fluoride ions.

Amino protected in the form of an azido group is converted into free amino, for example, by reduction, for example by catalytic hydrogenation with hydrogen in the presence of a hydrogenation catalyst, such as platinum oxide, palladium or Raney nickel, by reduction using mercapto compounds, such as dithiothreitol or mercaptoethanol, or by treatment with zinc in the presence of an acid, such as acetic acid. The catalytic hydrogenation is preferably carried out in an inert solvent, such as a halogenated hydrocarbon, for example methylene chloride, or in water or in a mixture of water and an organic solvent, such as an alcohol or dioxane, at approximately from 20°C to 25°C, or with cooling or heating.

A hydroxy or mercapto group protected by a suitable acyl group, by a tri-lower alkylsilyl group or by unsubstituted or substituted 1-phenyl-lower alkyl is freed analogously to a correspondingly protected amino group. A hydroxy or mercapto group protected by 2,2-dichloroacetyl is freed, for example, by basic hydrolysis, and a hydroxy or mercapto group protected by tertiary lower alkyl or by a 2-oxa- or 2-thia-aliphatic or -cycloaliphatic hydrocarbon radical is removed by acidolysis, for example by treatment with a mineral acid or a strong carboxylic acid, for example trifluoroacetic acid. Mercapto protected by pyridyldiphenylmethyl can be freed, for example, using mercury(H) salts at pH 2-6 or by zinc/acetic acid or by electrolytic reduction; acetamidomethyl and isobutyrylamidomethyl can be removed, for example, by reaction with mercury(H) salts at pH 2-6; 2-chloroacetamidomethyl can be removed, for example, using 1-piperidinothiocarboxamide; and S-ethylthio, S-tert-butylthio and S-sulfo can be cleaved, for example, by thiolysis with thiophenol, thioglycolic acid, sodium thiophenolate or 1,4-dithiothreitol. Two hydroxy groups or an adjacent amino and hydroxy group which are protected together by means of a bivalent protecting group, preferably, for example,

by a methylene group mono- or di-substituted by lower alkyl, such as lower alkylidene, for example isopropylidene, cycloalkylidene, for example cyclohexylidene, or benzylidene, can be freed by acid solvolysis, especially in the presence of a mineral acid or a strong organic acid. 2-Halo-lower alkoxy carbonyl is also removed using the above-mentioned reducing agents, for example a reducing metal, such as zinc, reducing metal salts, such as chromium(II) salts, or using sulfur compounds, for example sodium dithionite or preferably sodium sulfide and carbon disulfide.

When several protected functional groups are present, if desired the protecting groups may be so selected that more than one such group can be removed simultaneously, for example by acidolysis, such as by treatment with trifluoroacetic acid, or with hydrogen and a hydrogenation catalyst, such as a palladium-on-carbon catalyst. Conversely, the groups may also be so selected that they are not all removed simultaneously, but rather they are removed in a desired sequence or only some of them are removed.

In each of the processes mentioned above, the starting compounds may also be used in the form of salts, provided that the reaction conditions allow it.

Compounds of formula 1 obtainable in accordance with the process can be converted into different compounds of formula 1 in customary manner.

For example, in a compound of formula 1 obtainable in accordance with the process, hydroxymethyl X can be reduced reductively to methylene, for example by catalytic hydrogenation in the presence of palladium-on-carbon.

Futhermore, in a compound of formula 1 obtainable in accordance with the process, a carboxy group in free or reactive form may be esterified or amidated or an esterified or amidated carboxy group may be converted into a free carboxy group.

For the esterification or amidation of a carboxy group in a compound of formula 1, if desired the free acid can be used or the free acid can be converted into one of the above-mentioned reactive derivatives and reacted with an alcohol, with ammonia, or with a primary or secondary amine, or, in the case of esterification, the free acid or a reactive salt, for example the caesium salt, can be reacted with a reactive derivative of an alcohol. For example the caesium salt of a carboxylic acid can be reacted with a halide or sulfonic acid ester corresponding to the alcohol. The esterification of the carboxy group can also be carried out with other customary alkylating agents, for example with diazomethane, Meerwein salts or 1-substituted 3-aryltriazenes.

For the conversion of an esterified or amidated carboxy group into the free carboxy group it is possible to use one of the methods described above for the removal of carboxy-protecting groups or, if desired, alkaline hydrolysis in accordance with the reaction conditions mentioned in Organikum, 17th edition, VEB Deutscher Verlag der Wissenschaften, Berlin 1988.

In a compound of formula 1 obtainable in accordance with the process, an esterified carboxy group can be converted into an unsubstituted or substituted carboxamide group by aminolysis with ammonia or with a primary or secondary amine, optionally in the presence of a suitable condensation agent or catalyst. The aminolysis can be carried out in accordance with the reaction conditions mentioned for such reactions in Organikum, 15th edition, VEB Deutscher Verlag der Wissenschaften, Berlin (East) 1976.

A free amino group present in a compound of formula 1 obtainable in accordance with the process can be acylated or alkylated, for example to introduce a radical  $R_6$  other than hydrogen. The acylation and the alkylation can be carried out in

accordance with one of the methods mentioned for protecting groups or according to one of the processes mentioned in Organikum, 17th edition, VEB Deutscher Verlag der Wissenschaften, Berlin (East) 1988.

5 Furthermore, a free hydroxy group present in a compound of formula 1 obtainable in accordance with the process, for example as a constituent of the radical  $R_8$ , can be acylated. The acylation can be carried out with acylating reagents in accordance with one of the methods mentioned for protecting  
10 groups or according to one of the processes mentioned in Organikum, 17th edition, VEB Deutscher Verlag der Wissenschaften, Berlin (East) 1988.

In a compound of formula 1 obtainable in accordance with the process it is also possible to obtain from a sulfide the  
15 corresponding sulfoxide or sulfone, that is to say to oxidise a thio group to a sulfinyl or sulfonyl group or a sulfinyl group to sulfonyl, and also to oxidise thiomorpholino to S-oxy- or S,S-dioxy-thiomorpholino.

The oxidation to the sulfone can be carried out with most  
20 of the customary oxidising agents. It is especially preferable to use oxidising agents that oxidise the thio group or the sulfide sulfur selectively in the presence of other functional groups, for example amino or hydroxy groups, of the compound of formula 1 in question, for example aromatic or aliphatic  
25 peroxycarboxylic acids, for example peroxybenzoic acid, monoperphthalic acid, m-chloroperbenzoic acid, peracetic acid, performic acid or trifluoroperacetic acid. The oxidation with peroxycarboxylic acids is carried out in suitable solvents customarily used for that purpose, for example chlorinated  
30 hydrocarbons, for example methylene chloride or chloroform, ethers, such as diethyl ether, esters, such as ethyl acetate or the like, at temperatures of from  $-78^{\circ}\text{C}$  to room temperature, for example from  $-20^{\circ}\text{C}$  to  $+10^{\circ}\text{C}$ , preferably about  $0^{\circ}\text{C}$ . The

peroxycarboxylic acid can also be formed in situ, for example with hydrogen peroxide in acetic acid or formic acid that optionally contains acetic anhydride, for example with 30% or 90% hydrogen peroxide in acetic acid/acetic anhydride. Other

5 peroxo compounds are also suitable, for example potassium peroxomonosulfate in lower alkanol/water mixtures, for example methanol/water or ethanol/water, or in aqueous acetic acid at temperatures of from -70°C to +30°C, for example from -20°C to room temperature, and also sodium metaperiodate in methanol or  
10 methanol/water mixtures at temperatures of from 0°C to 50°C, for example about room temperature. If stoichiometric amounts of the mentioned oxidising agents are used it is also possible to obtain the corresponding sulfoxides.

If desired, it is possible by reduction of a sulfonyl group  
15 or a sulfone radical in an obtainable compound of formula 1 to obtain the corresponding thio compound or the corresponding sulfide, for example with diisobutylaluminium hydride in ether or tetrahydrofuran.

In compounds of formula 1 it is also possible to replace  
20 hydroxy R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and/or R<sub>4</sub> by one of the etherified hydroxy groups mentioned under formula 1 by reacting the corresponding compound of formula 1 wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and/or R<sub>4</sub> is hydroxy in customary manner, for example in the presence of a basic condensation agent, with a compound of the formula(e) R'<sub>1</sub> --Y,  
25 R'<sub>2</sub> --Y, R'<sub>3</sub> --Y and/or R'<sub>4</sub> --Y wherein R'<sub>1</sub> is lower alkyl or free or esterified or amidated carboxy-lower alkyl, R'<sub>2</sub> is lower alkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, optionally lower alkanoylated, halogenated or sulfonylated hydroxy-lower alkyl, oxo-lower  
30 alkyl, lower alkyl, lower alkenyl, cycloalkoxy-lower alkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkenyl, lower alkenyloxy-lower alkyl, lower alkenyloxy-lower alkyl, lower alkenyloxy-lower alkyl, lower alkanoyl-lower alkyl, optionally

S-oxidised lower alkyl-thio-lower alkyl, lower alkylthio-(hydroxy)-lower alkyl, aryl-lower alkyl, optionally hydrogenated heteroaryl-lower alkyl, optionally hydrogenated heteroarylthio-lower alkyl, cyano-lower alkyl or free or esterified or amidated carboxy-lower alkyl, R'<sub>3</sub> is lower alkyl, lower alkoxy-lower alkyl, hydroxy-lower alkyl, aryl-lower alkyl, halogenated lower alkyl, cyano-lower alkyl or free or esterified or amidated carboxy-lower alkyl, and R'<sub>4</sub> is lower alkyl, and Y is reactive esterified hydroxy, especially hydroxy esterified by a mineral acid, by sulfuric acid or by an organic sulfonic acid, such as halogen, preferably chlorine, bromine or iodine, groups of the formula O--SO<sub>2</sub>--O--R'<sub>A</sub>, or lower alkanesulfonyloxy or unsubstituted or substituted benzenesulfonyloxy, especially methane-, ethane-, benzene-, p-toluene- or p-bromobenzene-sulfonyl. The reaction is, as mentioned, preferably carried out in the presence of a basic condensation agent, such as an alkali metal carbonate, for example potassium carbonate, in an inert solvent, such as a lower alkanol, such as methanol, ethanol, butanol, tert-butanol or especially amyl alcohol, advantageously at elevated temperature, for example in a temperature range of approximately from 40° to 140°C, if necessary with removal of the resulting water of reaction by distillation, for example by azeotropic distillation.

It is also possible for salts of compounds of formula 1 obtainable in accordance with the process to be converted in a manner known per se into the free compounds, for example by treatment with a base, such as an alkali metal hydroxide, a metal carbonate or metal hydrogen carbonate, or ammonia, or another of the salt-forming bases mentioned at the beginning, or with an acid, such as a mineral acid, for example with hydrochloric acid, or another of the salt-forming acids mentioned at the beginning.



Resulting salts can be converted into different salts in a manner known per se: acid addition salts, for example, by treatment with a suitable metal salt, such as a sodium, barium or silver salt, of a different acid in a suitable solvent in which an inorganic salt being formed is insoluble and is therefore eliminated from the reaction equilibrium, and basic salts by freeing of the free acid and conversion into a salt again.

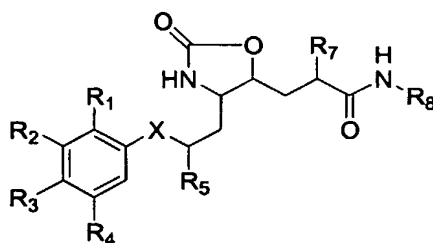
The compounds of formula 1, including their salts, may also be obtained in the form of hydrates or may include the solvent used for crystallisation.

As a result of the close relationship between the novel compounds in free form and in the form of their salts, hereinabove and hereinbelow any reference to the free compounds and their salts is to be understood as including also the corresponding salts and free compounds, respectively, as appropriate and expedient.

Stereoisomeric mixtures, that is to say mixtures of diastereoisomers and/or enantiomers, such as, for example, racemic mixtures, can be separated into the corresponding isomers in a manner known per se by suitable separating processes. For example, mixtures of diastereoisomers can be separated into the individual diastereoisomers by fractional crystallisation, chromatography, solvent partition etc.. Racemates can be separated from one another, after conversion of the optical antipodes into diastereoisomers, for example by reaction with optically active compounds, for example optically active acids or bases, by chromatography on column materials charged with optically active compounds or by enzymatic methods, for example by selective reaction of only one of the two enantiomers. This separation can be carried out either at the stage of one of the starting materials or with the compounds of formula 1 themselves.

In a compound of formula 1 the configuration at individual chirality centres can be selectively reversed. For example, the configuration of asymmetric carbon atoms that carry nucleophilic substituents, such as amino or hydroxy, can be reversed by  
5 second order nucleophilic substitution, optionally after conversion of the bonded nucleophilic substituent into a suitable nucleofugal leaving group and reaction with a reagent introducing the original substituent, or the configuration at carbon atoms having hydroxy groups can be reversed by oxidation  
10 and reduction, analogously to European Patent Application EP-A-0 236 734.

Also advantageous is the reactive functional modification of the hydroxy group and the subsequent replacement thereof by hydroxy with the configuration being reversed. For that purpose,  
15 the amino and hydroxy groups shown in formula 1 are bridged by a bivalent group, especially carbonyl, there being obtained a compound of formula XXVI



which can be cleaved again by treatment with thionyl  
20 chloride with the configuration being reversed.

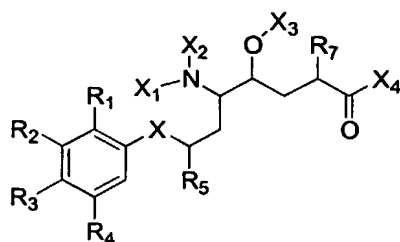
The invention relates also to those forms of the process in which a compound obtainable as intermediate at any stage is used as starting material and the remaining steps are carried out or the process is interrupted at any stage or a starting material  
25 is formed under the reaction conditions or is used in the form of a reactive derivative or salt, or a compound obtainable in accordance with the process of the invention is formed under the process conditions and further processed in situ. It is preferable to use those starting materials which result in the

compounds described above as being very preferred or very especially preferred.

The invention relates also to novel starting materials, which have been developed specifically for the preparation of the compounds according to the invention, especially the group of starting materials resulting in the compounds of formula 1 described at the beginning as being preferred, to processes for their preparation and to their use as intermediates.

This relates to compounds of formula II which, as mentioned, are suitable as intermediates for the preparation of compounds of formula 1.

The invention relates accordingly also to compounds of formula II



(II)

wherein  $R_1$  is hydrogen, hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy or free or esterified or amidated carboxy-lower alkoxy,

$R_2$  is hydrogen, lower alkyl, cycloalkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, hydroxy, optionally lower alkanoylated, halogenated or sulfonylated hydroxy-lower alkoxy; amino-lower alkyl that is unsubstituted or substituted by lower alkyl-, by lower alkanoyl- and/or by lower alkoxy-carbonyl; amino-lower alkoxy that is substituted by lower alkyl, by lower alkanoyl and/or by lower alkoxy-carbonyl; oxo-lower alkoxy, lower alkoxy, cycloalkoxy, lower alkenyloxy, cycloalkoxy-lower alkoxy, lower alkoxy-lower alkoxy, lower alkoxy-lower alkenyl, lower alkenyloxy-lower

alkoxy, lower alkoxy-lower alkoxy, lower alkenyloxy-lower alkyl, lower alkanoyl-lower alkoxy, optionally S-oxidised lower alkylthio-lower alkoxy, lower alkylthio-(hydroxy)-lower alkoxy, aryl-lower alkoxy, cyano-lower alkoxy, free or esterified or  
5 amidated carboxy-lower alkoxy or free or esterified or amidated carboxy-lower alkyl,

R<sub>3</sub> is optionally halogenated lower alkyl, lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, hydroxy-lower alkyl, optionally S-oxidised lower alkylthio-lower alkyl, optionally  
10 hydrogenated heteroaryl-lower alkyl, optionally hydrogenated heteroarylthio-lower alkyl; amino-lower alkyl that is unsubstituted or N-mono- or N,N-di-lower alkylated, N-lower alkanoylated or N-lower alkanesulfonylated or N,N-disubstituted by lower alkylene, by unsubstituted or N'-lower alkylated or N'-  
15 lower alkanoylated aza-lower alkylene, by oxa-lower alkylene or by optionally S-oxidised thia-lower alkylene; cyano-lower alkyl, free or esterified or amidated carboxy-lower alkyl, cycloalkyl, aryl, hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy, cycloalkoxy-lower alkoxy, hydroxy-lower alkoxy, aryl-  
20 lower alkoxy, optionally halogenated lower alkoxy, optionally S-oxidised lower alkylthio-lower alkoxy, optionally hydrogenated heteroaryl-lower alkoxy, optionally hydrogenated heteroarylthio-lower alkoxy; amino-lower alkoxy that is unsubstituted or N-mono- or N,N-di-lower alkylated, N-lower alkanoylated or N-lower  
25 alkanesulfonylated or substituted by lower alkylene, by unsubstituted or N'-lower alkylated or N'-lower alkanoylated aza-lower alkylene, by oxa-lower alkylene or by optionally S-oxidised thia-lower alkylene; cyano-lower alkoxy or free or esterified or amidated carboxy-lower alkoxy, or

30 R<sub>3</sub> together with R<sub>4</sub> is lower alkylenedioxy or a fused-on benzo or cyclohexeno ring,

R<sub>4</sub> together with R<sub>3</sub> is lower alkylenedioxy or a fused-on benzo or cyclohexeno ring, or is hydrogen, hydroxy or lower alkoxy,

X is methylene or hydroxymethylene,

5 R<sub>5</sub> is lower alkyl or cycloalkyl,

R<sub>7</sub> is lower alkyl or aryl-lower alkyl,

X<sub>1</sub> is an amino-protecting group,

X<sub>2</sub> is hydrogen or together with X<sub>3</sub> is a bivalent protecting group,

10 X<sub>3</sub> is hydrogen, a hydroxy-protecting group or together with X<sub>2</sub> is a bivalent protecting group or together with X<sub>4</sub> is a direct bond, and

X<sub>4</sub> is free or reactively etherified or esterified hydroxy or

15 X<sub>4</sub> together with X<sub>3</sub> is a direct bond and to the salts thereof,

to processes for the preparation thereof and to the use thereof as intermediates for the preparation of medicinal active ingredients, especially of formula 1.

20

In the compounds of formula II prepared according to the invention the variables R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, X, R<sub>5</sub> and R<sub>7</sub> are preferably as defined for formula 1, and the variables X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub> and X<sub>4</sub> are preferably as defined for formula II.

25 The invention relates especially to compounds of formula II wherein

R<sub>1</sub> is hydrogen, hydroxy, lower alkoxy, cycloalkoxy, lower alkoxy-lower alkoxy, carboxy-lower alkoxy, lower alkoxy-carbonyl-lower alkoxy, carbamoyl-lower alkoxy or N-

30 mono- or N,N-di-lower alkylcarbamoyl-lower alkoxy;

R<sub>2</sub> is hydrogen, lower alkyl, cycloalkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, hydroxy, lower alkanoyloxy-lower alkyl,

hydroxy-lower alkoxy, halo-(hydroxy)-lower alkoxy, lower  
alkanesulfonyl-(hydroxy)-lower alkoxy, amino-lower alkyl,  
lower alkylamino-lower alkyl, di-lower alkylamino-lower  
alkyl, lower alkanoylamino-lower alkyl, lower  
5 alkoxy-carbonyl-amino-lower alkyl, amino-lower alkoxy, lower  
alkylamino-lower alkoxy, di-lower alkylamino-lower alkoxy,  
lower alkanoylamino-lower alkoxy, lower alkoxy-carbonyl-  
amino-lower alkoxy, oxo-lower alkoxy, lower alkoxy,  
cycloalkoxy, lower alkenyloxy, cycloalkoxy-lower alkoxy,  
10 lower alkoxy-lower alkoxy, lower alkoxy-lower alkenyl,  
lower alkenyloxy-lower alkoxy, lower alkoxy-lower alkoxy,  
lower alkenyloxy-lower alkyl, lower alkanoyl-lower alkoxy,  
lower alkylthio-lower alkoxy, lower alkane-sulfonyl-lower  
alkoxy, lower alkylthio-(hydroxy)-lower alkoxy, aryl-lower  
15 alkoxy, thiazolylthio-lower alkoxy or thiazolinylthio-lower  
alkoxy, imidazolylthio-lower alkoxy, optionally N-oxidised  
pyridylthio-lower alkoxy, pyrimidinylthio-lower alkoxy,  
cyano-lower alkoxy, lower alkoxy-carbonyl-lower alkoxy,  
carbamoyl-lower alkoxy, N-mono- or N,N-di-lower  
20 alkylcarbamoyl-lower alkoxy, carboxy-lower alkyl, lower  
alkoxy-carbonyl-lower alkyl, carbamoyl-lower alkyl or N-  
mono- or N,N-di-lower alkylcarbamoyl-lower alkyl;

R<sub>3</sub> is lower alkyl, polyhalo-lower alkyl, lower alkoxy-lower  
alkyl, cycloalkoxy-lower alkyl, hydroxy-lower alkyl, lower  
25 alkylthio-lower alkyl, lower alkanesulfonyl-lower alkyl,  
optionally partially hydrogenated or N-oxidised pyridyl-  
lower alkyl, thiazolyl-thio-lower alkyl or thiazolinylthio-  
lower alkyl, imidazolylthio-lower alkyl, optionally N-  
oxidised pyridylthio-lower alkyl, pyrimidinylthio-lower  
30 alkyl, amino-lower alkyl, lower alkylamino-lower alkyl, di-  
lower alkylamino-lower alkyl, lower alkanoyl-amino-lower  
alkyl, lower alkanesulfonylamino-lower alkyl, polyhalo-  
lower alkane-sulfonylamino-lower alkyl, pyrrolidino-lower

alkyl, piperidino-lower alkyl, piperazino-, N'-lower  
alkylpiperazino- or N'-lower alkanoylpiperazino-lower  
alkyl, morpholino-lower alkyl, thiomorpholino-, S-  
oxothiomorpholino- or S,S-dioxothio-morpholino-lower alkyl,  
5 cyano-lower alkyl, carboxy-lower alkyl, lower alkoxy-  
carbonyl-lower alkyl, carbamoyl-lower alkyl, N-mono- or  
N,N-di-lower alkyl-carbamoyl-lower alkyl, cycloalkyl;  
phenyl or naphthyl that is unsubstituted or mono-, di- or  
tri-substituted by lower alkyl, lower alkoxy, hydroxy,  
10 lower alkylamino, di-lower alkylamino, halogen and/or by  
trifluoromethyl; hydroxy, lower alkoxy, cyclo-alkoxy, lower  
alkoxy-lower alkoxy, cycloalkoxy-lower alkoxy, hydroxy-  
lower alkoxy; phenyl-lower alkoxy or naphthyl-lower alkoxy  
that is unsubstituted or mono-, di- or tri-substituted by  
15 lower alkyl, lower alkoxy, hydroxy, lower alkylamino, di-  
lower alkylamino, halogen and/or by trifluoromethyl; lower  
alkoxy, polyhalo-lower alkoxy, lower alkylthio-lower  
alkoxy, lower alkanesulfonyl-lower alkoxy, optionally  
hydrogenated heteroaryl-lower alkoxy, optionally partially  
20 or fully hydrogenated heteroarylthio-lower alkoxy, such as  
thiazolylthio-lower alkoxy or thiazolinythio-lower alkoxy,  
imidazolylthio-lower alkoxy, optionally N-oxidised  
pyridylthio-lower alkoxy, pyrimidinylthio-lower alkoxy,  
amino-lower alkoxy, lower alkylamino-lower alkoxy, di-lower  
25 alkylamino-lower alkoxy, lower alkanoylamino-lower alkoxy,  
lower alkanesulfonylamino-lower alkoxy, polyhalo-lower  
alkanesulfonylamino-lower alkoxy, pyrrolidino-lower alkoxy,  
piperidino-lower alkoxy, piperazino-, N'-lower  
alkylpiperazino- or N'-lower alkanoylpiperazino-lower  
30 alkoxy, morpholino-lower alkoxy, thiomorpholino-, S-  
oxothiomorpholino- or S,S-dioxothiomorpholino-lower alkoxy,  
cyano-lower alkoxy, carboxy-lower alkoxy, lower  
alkoxycarbonyl-lower alkoxy, carbamoyl-lower alkoxy or N-

mono- or N,N-di-lower alkylcarbamoyl-lower alkoxy, or together with R<sub>4</sub> is lower alkylenedioxy or a fused-on benzo or cyclohexeno ring;

R<sub>4</sub> together with R<sub>3</sub> is lower alkylenedioxy or a fused-on benzo or cyclohexeno ring, or is hydrogen, hydroxy or lower alkoxy;

X is methylene or hydroxymethylene;

R<sub>5</sub> is lower alkyl or cycloalkyl;

R<sub>7</sub> is lower alkyl, or phenyl-lower alkyl that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen, nitro and/or by amino;

X<sub>1</sub> is lower alkoxycarbonyl, or  $\alpha$ -phenyl- or  $\alpha,\alpha$ -diphenyl-lower alkoxycarbonyl that is unsubstituted or substituted by lower alkyl, lower alkoxy, nitro and/or by halogen, or is 2-halo-lower alkoxycarbonyl;

X<sub>2</sub> is hydrogen; or

X<sub>2</sub> together with X<sub>3</sub> is carbonyl or lower alkylidene,

X<sub>3</sub> is hydrogen, tri-lower alkylsilyl or together with X<sub>2</sub> is carbonyl or lower alkylidene; or

X<sub>3</sub> together with X<sub>4</sub> is a direct bond,

X<sub>4</sub> is lower alkoxy, phenyl-lower alkoxy or hydroxy; or

X<sub>4</sub> together with X<sub>3</sub> is a direct bond, and the salts thereof.

The invention relates more especially to compounds of formula II wherein

R<sub>1</sub> is hydrogen;

R<sub>2</sub> is lower alkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkoxy, lower alkoxy-lower alkoxy-lower alkyl; phenyl-lower alkoxy that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen, nitro and/or by amino; optionally N-oxidised pyridyl-lower alkoxy, lower alkylthio-lower alkoxy, lower alkane-sulfonyl-lower alkoxy, lower alkanoyl-lower alkoxy, optionally N-oxidised pyridyl-



lower alkoxy, cyano-lower alkoxy, carboxy-lower alkoxy,  
 lower alkoxycarbonyl-lower alkoxy, carbamoyl-lower alkoxy,  
 lower alkylcarbamoyl-lower alkoxy or di-lower  
 alkylcarbamoyl-lower alkoxy,

5  $R_3$  is hydrogen, lower alkyl, hydroxy, lower alkoxy or polyhalo-  
 lower alkoxy; or

$R_3$  together with  $R_4$  is lower alkylenedioxy;

X is methylene or hydroxymethylene;

$R_5$  is lower alkyl or cycloalkyl;

10  $R_7$  is lower alkyl;

$X_1$  is lower alkoxycarbonyl, or .alpha.-phenyl-lower  
 alkoxycarbonyl that is unsubstituted or substituted by  
 lower alkyl, lower alkoxy, nitro and/or by halogen;

$X_2$  is hydrogen or together with  $X_3$  is lower alkylidene;

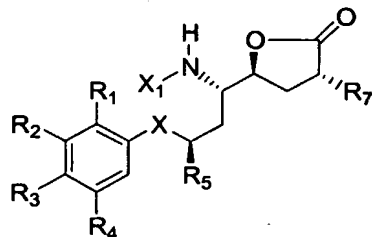
15  $X_3$  is hydrogen or together with  $X_2$  is lower alkylidene; or

$X_3$  together with  $X_4$  is a direct bond; and

$X_4$  is hydroxy or together with  $X_3$  is a direct bond;

and the salts thereof.

20 The invention relates especially to compounds of formula II  
 wherein at least one, for example one, two or preferably all, of  
 the asymmetric carbon atoms of the main chain have the  
 stereochemical configuration shown in formula IIId



(IIId)

25 the variables each being as defined above, and the salts  
 thereof.

The invention relates very especially to compounds of  
 formula IIId wherein

R<sub>1</sub> and R<sub>4</sub> are hydrogen,

R<sub>2</sub> is C<sub>1</sub>-C<sub>4</sub> alkoxy-C<sub>1</sub>-C<sub>4</sub> alkoxy, such as 3-methoxypropyloxy, or  
C<sub>1</sub>-C<sub>4</sub> alkoxy-C<sub>1</sub>-C<sub>4</sub>-alkyl, such as 3-methoxybutyl,

R<sub>3</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl, such as isopropyl or tert-butyl, or C<sub>1</sub>-C<sub>4</sub>  
5 alkoxy, such as methoxy,

X is methylene,

R<sub>5</sub> and R<sub>7</sub> are branched C<sub>1</sub>-C<sub>4</sub> alkyl, such as isopropyl, and

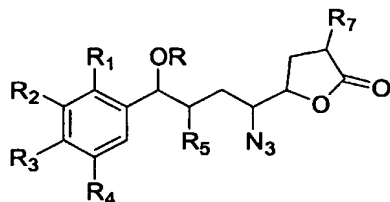
X<sub>1</sub> is C<sub>1</sub>-C<sub>7</sub> alkoxycarbonyl, such as tert-butoxycarbonyl,  
and the salts thereof.

10

The invention relates specifically to the compounds of  
formulae II and IIId mentioned in the Examples and the salts  
thereof.

The process according to the invention for the preparation  
15 of compounds of formula II is as follows:

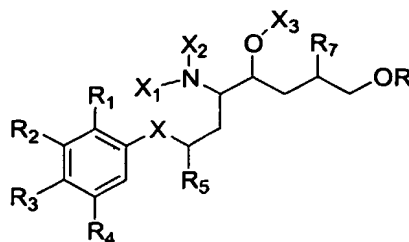
d) for the preparation of compounds of formula IIc, in a  
compound of formula XVI



wherein R is a hydroxy-protecting group, the azido group is  
20 reduced to amino and, if desired, hydroxy is freed from the  
group --OR or the group --OR is replaced reductively by  
hydrogen, and the protecting group X<sub>1</sub> is introduced, and

e) for the preparation of compounds of formula IIa, a  
compound of formula IIc is hydrolysed in customary manner, the  
25 hydroxy-protecting group X<sub>3</sub> is introduced and, if desired, the  
terminal carboxy group is reactively modified, or

f) for the preparation of compounds of formula IIb, in a  
compound of formula XIX



the terminal hydroxy group is freed reductively and the terminal hydroxymethyl group is first converted into formyl in customary manner, for example as indicated under Process variant  
 5 a), and the formyl group formed is oxidised to the acid in customary manner or the terminal hydroxy group is oxidised directly to the acid, and, if desired, the carboxy function is reactively modified, if necessary any protecting groups present are removed and, if desired, the compound obtainable in  
 10 accordance with the process is converted into a salt or a salt obtainable in accordance with the process is converted into the free compound or into a different salt and/or mixtures of isomers that may be obtainable are separated.

The starting materials of formulae XVI and XIX are  
 15 prepared, for example, as indicated under Process variant a).

Compounds of formula II obtainable in accordance with the process can be converted into different compounds of formula II in customary manner.

For example, in a compound of formula II obtainable in  
 20 accordance with the process, hydroxymethyl X can be reduced reductively to methylene, for example by catalytic hydrogenation in the presence of palladium-on-carbon.

Furthermore, in a compound of formula II obtainable in accordance with the process, a carboxy group in free or reactive  
 25 form may be esterified or amidated or an esterified or amidated carboxy group may be converted into a free carboxy group.

For the esterification or amidation of a carboxy group in a compound of formula II, if desired the free acid can be used or the free acid can be converted into one of the above-mentioned

reactive derivatives and reacted with an alcohol, with ammonia, or with a primary or secondary amine, or in the case of esterification, the free acid or a reactive salt, for example the caesium salt, can be reacted with a reactive derivative of an alcohol. For example the caesium salt of a carboxylic acid can be reacted with a halide or sulfonic acid ester corresponding to the alcohol. The esterification of the carboxy group can also be carried out using other customary alkylating agents, for example with diazomethane, Meerwein salts or 1-substituted 3-aryltriazenes.

For the conversion of an esterified or amidated carboxy group into the free carboxy group it is possible to use one of the methods described above for the removal of carboxy-protecting groups or, if desired, alkaline hydrolysis in accordance with the reaction conditions mentioned in Organikum, 17th edition, VEB Deutscher Verlag der Wissenschaften, Berlin 1988.

In compounds of formula II it is also possible to replace hydroxy  $R_1$ ,  $R_2$ ,  $R_3$  and/or  $R_4$  by one of the etherified hydroxy groups mentioned under formula II by reacting the corresponding compound of formula II wherein  $R_1$ ,  $R_2$ ,  $R_3$  and/or  $R_4$  is hydroxy in customary manner, for example in the presence of a basic condensation agent, with a compound of the formula(e)  $R'_1$  --Y,  $R'_2$  --Y,  $R'_3$  --Y and/or  $R'_4$  --Y wherein  $R'_1$  is lower alkyl or free or esterified or amidated carboxy-lower alkyl,  $R'_2$  is lower alkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkoxy-lower alkyl, cycloalkoxy-lower alkyl, optionally lower alkanoylated, halogenated or sulfonylated hydroxy-lower alkyl, oxo-lower alkyl, lower alkyl, lower alkenyl, cycloalkoxy-lower alkyl, lower alkoxy-lower alkyl, lower alkoxy-lower alkenyl, lower alkenyloxy-lower alkyl, lower alkenyloxy-lower alkyl, lower alkenyloxy-lower alkyl, lower alkanoyl-lower alkyl, optionally S-oxidised lower alkyl-thio-lower alkyl, lower alkylthio-

(hydroxy)-lower alkyl, aryl-lower alkyl, optionally hydrogenated heteroaryl-lower alkyl, optionally hydrogenated heteroarylthio-lower alkyl, cyano-lower alkyl or free or esterified or amidated carboxy-lower alkyl,  $R'_3$  is lower alkyl, lower alkoxy-lower alkyl, hydroxy-lower alkyl, aryl-lower alkyl, halogenated lower alkyl, cyano-lower alkyl or free or esterified or amidated carboxy-lower alkyl, and  $R'_4$  is lower alkyl, and Y is reactive esterified hydroxy, especially hydroxy esterified by a mineral acid, by sulfuric acid or by an organic sulfonic acid, such as halogen, preferably chlorine, bromine or iodine, groups of the formula  $O--SO_2--O--R'_A$ , or lower alkanesulfonyloxy or unsubstituted or substituted benzenesulfonyloxy, especially methane-, ethane-, benzene-, p-toluene- or p-bromobenzene-sulfonyl. The reaction is, as mentioned, preferably carried out in the presence of a basic condensation agent, such as an alkali metal carbonate, for example potassium carbonate, in an inert solvent, such as a lower alkanol, such as methanol, ethanol, butanol, tert-butanol or especially amyl alcohol, advantageously at elevated temperature, for example in a temperature range of approximately from 40° to 140°C., if necessary with removal of the resulting water of reaction by distillation, for example by azeotropic distillation.

It is also possible for salts of compounds of formula II obtainable in accordance with the process to be converted in a manner known per se into the free compounds, for example by treatment with a base, such as an alkali metal hydroxide, a metal carbonate or metal hydrogen carbonate, or ammonia, or another of the salt-forming bases mentioned at the beginning, or with an acid, such as a mineral acid, for example with hydrochloric acid, or another of the salt-forming acids mentioned at the beginning.

Resulting salts can be converted into different salts in a manner known per se: acid addition salts, for example, by

treatment with a suitable metal salt, such as a sodium, barium or silver salt, of a different acid in a suitable solvent in which an inorganic salt being formed is insoluble and is therefore eliminated from the reaction equilibrium, and basic salts by freeing of the free acid and conversion into a salt again.

The compounds of formula II, including their salts, may also be obtained in the form of hydrates or may include the solvent used for crystallisation.

10 As a result of the close relationship between the novel compounds in free form and in the form of their salts, hereinabove and hereinbelow any reference to the free compounds and their salts is to be understood as including also the corresponding salts and free compounds, respectively, as  
15 appropriate and expedient.

The following Examples serve to illustrate the invention; temperatures are given in degrees Celsius, pressures in mbar.

HPLC--column dimensions: 250 x 4.6 mm

HPLC--column packing: Nucleosil® 5C<sub>18</sub>

20 HPLC--eluant: A) water+0.1% by vol. trifluoroacetic acid B) acetonitrile+0.1% by vol. trifluoroacetic acid

HPLC--gradient 0: 20-100% B in 20 minutes+8 minutes 100% B

HPLC--gradient I: linear in 60 minutes from 30% by vol. B+70% by vol. A to 90% by vol. B +10% by vol. A

25 The abbreviation "R<sub>f</sub> (A)" means, for example, that the R<sub>f</sub> value was determined in solvent system A. The quantity ratio of solvents to one another is always given in parts by volume. The same abbreviations are used for indicating the eluant systems for flash chromatography and medium pressure  
30 chromatography.

Mass-spectroscopic measurements are obtained either by conventional MS or in accordance with the "Fast-Atom-Bombardment" (FAB-MS) method. In the former case the mass data

relate to the unprotonated molecule ion (M)<sup>+</sup> or the protonated molecule ion (M+H)<sup>+</sup>.

The short names and abbreviations used have the following meanings:

C<sub>18</sub> -Nucleosil® brand name for reversed phase column material for HPLC charged with octadecyl radicals (Nucleosil® 5C<sub>18</sub>, Macherey & Nagel, FRG)

pFAB-MS Fast-Atom-Bombardment mass spectroscopy

FC flash chromatography

HPLC high performance liquid chromatography

Hyflo® brand name for filter aids (Fluka, Buchs, Switzerland)

IR infrared spectroscopy

b.p. at the pressure indicated in torr

ml milliliters

MS mass spectroscopy

R<sub>f</sub> ratio of the migration of a substance to the distance of the eluant front from the starting point in TLC

R<sub>t</sub> retention time of a substance in HPLC (in minutes)

m.p. melting point (temperature).

#### EXAMPLE 1

2 (R,S) -Methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- (p-tert-butylphenyl) -octanoic acid (N-butyl)amide hydrochloride

111 mg of N-tert-butoxycarbonyl-2 (R,S) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- (p-tert-butyl-phenyl) -octanoic acid (N-butyl)amide are dissolved in 2 ml of 4N hydrochloric acid in dioxane at 0°C and then stirred for 60 minutes at 20°C. The reaction mixture is concentrated by evaporation under reduced pressure and the residue is purified by means of FC (50 g of silica gel, dichloromethane/methanol=9:1). The title compound is

obtained in the form of a diastereoisomeric mixture:  $R_f$  (dichloromethane/methanol=9:1)=0.20;  $R_t$  (I)=36.6 and 37.5 minutes; FAB-MS  $(M+H)^+ = 419$ .

5 The starting materials are prepared as follows:

a) N-Tert-butoxycarbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(p-tert-butyl-phenyl)-octanoic acid (N-butyl)amide

150 mg of N-tert-butoxycarbonyl-2-methylene-4(S)-hydroxy-  
10 5(S)-amino-7(S)-isopropyl-8-(p-tert-butyl-phenyl)-octanoic acid (N-butyl)amide (diastereoisomer I) are hydrogenated in the presence of 150 mg of 10% Pd/C in 20 ml of tetrahydrofuran for 2 hours at room temperature and under normal pressure. The reaction mixture is filtered and concentrated by evaporation.  
15 The residue is purified by means of FC (50 g of silica gel, dichloromethane/diethyl ether=8:2). The title compound is obtained in the form of a diastereoisomeric mixture:  $R_f$  (dichloromethane/diethyl ether=8:2)=0.18.

20 b) N-Tert-butoxycarbonyl-2-methylene-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(p-tert-butyl-phenyl)-octanoic acid (N-butyl)amide

695 mg of methacrylic acid butylamide are dissolved in 30 ml of tetrahydrofuran and, at  $-75^\circ\text{C}$ , 6.2 ml of 1.6 M n-  
25 butyllithium in hexane are added thereto. The reaction mixture is stirred for 30 minutes at  $0^\circ\text{C}$  and then, at  $-75^\circ\text{C}$ , 9.8 ml of 1 M chlorotitanium triisopropoxide in hexane are added thereto. The mixture is stirred for a further 15 minutes at  $-75^\circ\text{C}$  and then, at the same temperature, a solution of 924 mg of 2(S)-  
30 tert-butoxy-carbonyl-amino-4(S)-isopropyl-5-(p-tert-butyl-phenyl)-pentanal in 10 ml of tetrahydrofuran is added dropwise thereto. The reaction mixture is then stirred further for 15 minutes at  $-75^\circ\text{C}$  and for 70 minutes at  $0^\circ\text{C}$  and then, in



succession, 15 ml of 10% aqueous citric acid solution, water and diethyl ether are added thereto. The product is extracted repeatedly with diethyl ether. The diastereoisomeric mixture is separated by FC (700 g of silica gel, eluant:

5 dichloromethane/diethyl ether=9:1). The title compound is obtained:

diastereoisomer I:

$R_f$  (dichloromethane/diethyl ether=9:1)=0.21;

diastereoisomer II:

10  $R_f$  (dichloromethane/diethyl ether=9:1)=0.14.

c) 2(S)-Tert-butoxycarbonylamino-4(S)-isopropyl-5-(p-tert-butyl-phenyl)-pentanal

At -75°C, 4.2 ml of 1.2 M diisobutylaluminium hydride  
15 solution in toluene are slowly added dropwise to a solution of 1 g of 2(S)-tert-butoxycarbonylamino-4(S)-isopropyl-5-(p-tert-butyl-phenyl)-pentanoic acid methyl ester in 20 ml of toluene. The reaction mixture is then stirred for a further 30 minutes at -70°C, 10 ml of methanol are added, the mixture is poured onto a  
20 mixture of ice and 10 ml of 1N hydrochloric acid, and extraction is carried out with ethyl acetate. The title compound is obtained:  $R_f$  (dichloromethane)=0.35.

d) 2(S)-Tert-butoxycarbonylamino-4(S)-isopropyl-5-(p-tert-butyl-phenyl)-pentanoic acid methyl ester  
25

To a solution of 2.6 g of 2(S)-amino-4(S)-isopropyl-5-(p-tert-butyl-phenyl)-pentanoic acid methyl ester in 50 ml of dichloromethane there are added dropwise at 0°C. 2 ml of  
30 ethyldiisopropylamine and then a solution of 2.4 g of di-tert-butyl dicarbonate in 10 ml of dichloromethane. The reaction mixture is stirred for 16 hours at room temperature and then

concentrated by evaporation. The title compound is obtained by FC (240 g of silica gel, eluant: dichloromethane):

$R_f$  (dichloromethane)=0.50.

- 5           e) 2(S)-Amino-4(S)-isopropyl-5-(p-tert-butyl-phenyl)-pentanoic acid methyl ester

With stirring at room temperature, 36 ml of 1N hydrochloric acid am added to a solution of 3.55 g of 2(R)-isopropyl-5(S)-  
10 [2(S)-isopropyl-3-(p-tert-butylphenyl)-propyl]-2,5-dihydro-3,6-dimethoxy-pyrazine in 35 ml of acetonitrile and the mixture is then stirred for a further 3 hours. The reaction solution is then poured onto a mixture of 45 ml of saturated  $\text{NaHCO}_3$  solution and ice and the suspension is extracted with dichloromethane.  
15 The extracts are concentrated by evaporation and purified by FC (700 g of silica gel, eluant: dichloromethane/methanol/ $\text{NH}_3$  =200:10:1), yielding the title compound:  $R_f$  (dichloromethane/methanol/conc. ammonia=200:10:1)=0.70.

- 20           f) 2(R)-Isopropyl-5(S)-[2(S)-isopropyl-3-(p-tert-butyl-phenyl)-propyl]-2,5-dihydro-3,6-dimethoxypyrazine

To a solution of 2.6 ml of 2(R)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-pyrazine in 30 ml of tetrahydrofuran there are added  
25 dropwise, with stirring at  $-70^\circ\text{C}$ , 8.2 ml of 1.6 M butyl-lithium solution in hexane and, after a further 15 minutes' stirring, a solution of 2.8 g of 1-bromo-2(R)-isopropyl-3-(p-tert-butyl-phenyl)-propane in 10 ml of tetrahydrofuran. The reaction mixture is stirred further for 2 hours at  $-70^\circ\text{C}$  and for 3 hours  
30 at  $-25^\circ\text{C}$ , is left to stand for 20 hours at  $-10^\circ\text{C}$  and is then concentrated by evaporation. Saturated ammonium chloride solution and water are added to the residue and extraction is carried out with diethyl ether. The extracts are concentrated by

evaporation and purified by FC (200 g of silica gel, eluant: dichloromethane/hexane=1:1). The title compound is obtained:  $R_f$  (dichloromethane/hexane=1:1)=0.30.

5 g) 1-Bromo-2(R)-isopropyl-3-(p-tert-butyl-phenyl)-propane

To a solution of 2.3 g of 2(R)-isopropyl-3-(p-tert-butyl-phenyl)-propanol in 50 ml of dichloromethane there are added, with stirring at 0°C, 3.15 g of triphenylphosphine and then, in  
10 portions, 2.14 g of N-bromosuccinimide. The reaction mixture is subsequently stirred for 16 hours at room temperature and is then concentrated by evaporation. The residue is purified by FC (100 g of silica gel, eluant; dichloromethane/hexane=1:1). The title compound is obtained:  $R_f$  (hexanes)=0.49.

15

h) 2(R)-Isopropyl-3-(p-tert-butyl-phenyl)-propanol

With stirring at 0°C, a solution of 8.63 g of 3-[2(R)-isopropyl-3-(p-tert-butyl-phenyl)-propanoyl]-4(R)-benzyl-oxazolidin-2-one in 40 ml of tetrahydrofuran is added dropwise  
20 to a suspension of 2.41 g of  $\text{LiAlH}_4$  in 160 ml of tetrahydrofuran. The reaction mixture is stirred for a further 4 hours at 0°C and then, at 0°C, 5 ml of ethyl acetate, 30 ml of a mixture of tetrahydrofuran/water=1:1 and then 80 ml of 2N  
25 sulfuric acid are added in succession thereto. The suspension is extracted with ethyl acetate and the extracts are concentrated by evaporation and purified by FC (700 g of silica gel, eluant: dichloromethane). The title compound is obtained:

$R_f$  (dichloromethane)=0.34; m.p.=49°-51°C.

30

i) 3-[2(R)-Isopropyl-3-(p-tert-butyl-phenyl)-propionyl]-4(R)-benzyl-oxazolidin-2-one

30 ml of tetrahydrofuran are added to a solution of 31 ml of 1 M lithium hexamethyl-disilazide and the mixture is stirred at -70°C. A solution of 3-isovaleroyl-4(R)-benzyloxazolidin-2-one in 20 ml of tetrahydrofuran is then added dropwise thereto and the reaction mixture is stirred for a further 1 hour at -70°C. A solution of 9.6 g of p-tert-butyl-benzyl bromide in 20 ml of tetrahydrofuran is then added dropwise thereto and the reaction mixture is stirred for a further 1 hour at -25°C and then for 4 hours at 0°C. 6 ml of saturated ammonium chloride solution are then added to the reaction mixture, which is freed of tetrahydrofuran by means of concentration and then subjected to extraction with diethyl ether. The extract is concentrated by evaporation and the residue is purified by FC (700 g of silica gel, eluant: dichloromethane/hexane=1:1), yielding the title compound:

$R_f$  (dichloromethane/hexane=1:1)=0.30; m.p.=123.5-124°C.

#### EXAMPLE 2

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-ethyl-8-(p-tert-butyl-phenyl)-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from N-tert-butoxycarbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-ethyl-8-(p-tert-butyl-phenyl)-octanoic acid (N-butyl)amide and is purified by FC (20 g of silica gel, eluant: dichloromethane/methanol=95:5). Title compound:

$R_f$  (dichloromethane/methanol=95:5)=0.09;  $R_t$  (I)=43.31 minutes; FAB-MS  $(M+H)^+ = 405$ .

The starting material is prepared analogously to Example 1, except that in step i) instead of 3-isovaleroyl-4(R)-benzyloxazolidin-2-one there is used 3-butyroyl-4(R)-benzyloxazolidin-2-one.

**EXAMPLE 3**

2 (R,S) -Methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -methyl-8-  
biphenyl-octanoic acid (N-butyl)amide hydrochloride

5 Analogously to Example 1, the title compound is prepared  
starting from 100 mg of N-tert-butoxycarbonyl-2 (R,S) -methyl-  
4 (S) -hydroxy-5 (S) -amino-7 (S) -methyl-8- biphenyl-octanoic acid  
(N-butyl)amide and is purified by FC (50 g of silica gel,  
eluant: dichloromethane/methanol=9:1). This yields the pure  
10 title compound:  $R_f$  (dichloromethane/methanol=9:1)=0.11;  $R_t$   
(I)=29 minutes; FAB-MS  $(M+H)^+ = 411$ .

The starting material is obtained analogously to Example 1,  
except that in step i) instead of 3-isovaleroyl-4 (R) -benzyl-  
oxazolidin-2-one there is used 3-propionyl-4 (R) -benzyl-  
15 oxazolidin-2-one and instead of p-tert-butyl-benzyl bromide  
there is used p-phenylbenzyl bromide.

**EXAMPLE 4**

2 (R,S) -Methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -ethyl-8- (4-  
20 propyloxymethyl-naphth-2-yl)-octanoic acid (N-butyl)amide  
hydrochloride

Analogously to Example 1, the title compound is prepared  
starting from 51 mg of N-tert-butoxycarbonyl-2 (R,S) -methyl-4 (S) -  
25 hydroxy-5 (S) -amino-7 (S) -ethyl-8- ( 4-propyloxy-methyl-naphth-2-  
yl)-octanoic acid (N-butyl)amide and is purified by means of FC  
(15 g of silica gel, eluant: dichloromethane/methanol=8:2).  
Title compound:  $R_f$  (dichloromethane/methanol=8:2)=0.48; FAB-MS  
(M+H)<sup>+</sup> =471.

30

The starting material is obtained analogously to Example 1,  
step i) being altered as follows:

3-[2(S)-Ethyl-3-(4-propyloxymethyl-naphth-2-yl)-propionyl]-  
4(R)-benzyl-oxazolidin-2-one:

30 ml of tetrahydrofuran and a solution of 2.97 g of 3-  
5 butyroyl-4(R)-benzyl-oxazolidin-2-one in 15 ml of  
tetrahydrofuran are added dropwise in succession to a solution,  
stirred at -75°C, of 12 ml of 1 M lithium hexamethyldisilazide  
solution. The reaction mixture is stirred for 1 hour at -75°C, a  
10 solution of 3.52 g of 4-propoxymethyl-2-bromomethyl-naphthalene  
in 15 ml of tetrahydrofuran is added dropwise thereto and the  
mixture is then stirred further for 1 hour at -30°C and for 3  
hours at 0°C. After the dropwise addition at 0°C of 2.7 ml of  
saturated ammonium chloride solution, the reaction mixture is  
15 concentrated by evaporation and the residue is partitioned  
between diethyl ether and water. The organic extracts are  
concentrated by evaporation and the residue is purified by FC (1  
kg of silica gel, eluant: dichloromethane/hexane=3:1), yielding  
the title compound:  $R_f$  (dichloromethane/hexane=3:1)=0.24; FAB-MS  
(M+Na)<sup>+</sup> =482.

#### EXAMPLE 5

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-  
hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide  
hydrochloride

30 mg of N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-  
5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-  
octanoic acid (N-butyl)amide are treated with 0.6 ml of 4N  
hydrochloric acid in dioxane analogously to Example 1 and the  
30 product is purified by means of FC (15 g of silica gel,  
dichloromethane/methanol=9:1). The title compound is obtained:  
 $R_f$  (dichloromethane/methanol=9:1)=0.17;  $R_t$  (I)=28.54 minutes;  
FAB-MS (M+H)<sup>+</sup> =435.

The starting materials are prepared as follows:

a) N-Tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-  
5 amino-7(S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic  
acid (N-butyl)amide

860 mg of N-tert-butoxycarbonyl-2-methylene-4(S)-hydroxy-  
5(S)-amino-7(S)-isopropyl-8-(3-benzyloxy-4-tert-butyl-phenyl)-  
octanoic acid (N-butyl)amide are hydrogenated for 3 hours at  
10 room temperature and under normal pressure in the presence of  
860 mg of 50% Pd/C in 30 ml of methanol. The reaction mixture is  
filtered and concentrated by evaporation. The residue is  
purified by means of FC (100 g of silica gel,  
dichloromethane/ethyl acetate=9:1) with separation of the  
15 diastereoisomers. The title compound is obtained:  
 $R_f$  (dichloromethane/ethyl acetate=8:2)=0.23.

The unseparated diastereoisomeric mixture N-tert-  
butoxycarbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-  
20 isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-  
butyl)amide has an  $R_f$  (ethyl acetate/hexane=1:1) of 0.38.

a') N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-  
amino-7(S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic  
25 acid (N-butyl)amide can also be prepared as follows:

175 mg of N-tert-butoxycarbonyl-2-methylene-4(S)-hydroxy-  
5(S)-amino-7(S)-isopropyl-8-(3-benzyloxy-4-tert-butyl-phenyl)-  
octanoic acid (N-butyl)amide are hydrogenated in the presence of  
30 12 mg of  $[Ru_2 Cl_4 (S-Binap)_2] \cdot (NEt_3)$  in 30 ml of methanol for 20  
hours at room temperature and under 30 bar. The reaction mixture  
is filtered, concentrated by evaporation and purified by means  
of FC (hexane/ethyl acetate=1:1). The title compound so obtained

( $R_f$  in hexane/ethyl acetate=1:1)=0.15 is deprotected by hydrogenation with 90 mg of 10% Pd/C in 10 ml of methanol at room temperature and under normal pressure to form N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-  
5 isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide.

The starting material is prepared analogously to Example 1, steps b) to g), the 2(S)-isopropyl-3-(3-benzyloxy-4-tert-butyl-phenyl)-propanol used in step g) being prepared as follows:  
10

h) 2(R)-Isopropyl-3-(3-benzyloxy-4-tert-butyl-phenyl)-propanol

15 At room temperature with stirring, to a solution of 5.65 g of 2(R)-isopropyl-3-(3-hydroxy-4-tert-butyl-phenyl)-propanol in 100 ml of dimethylformamide there are added 11 g of caesium carbonate and, dropwise, a solution of 3.2 ml of benzyl bromide in 20 ml of dimethylformamide. The reaction mixture is stirred  
20 at room temperature for a further 16 hours and then concentrated by evaporation, and the residue is partitioned between diethyl ether and water. The organic phases are concentrated by evaporation and the residue is purified by FC (90 g of silica gel, dichloromethane/hexane=9:1), yielding the title compound:  
25  $R_f$  (dichloromethane/hexane=9:1)=0.44.

i) 2(R)-Isopropyl-3-(3-hydroxy-4-tert-butyl-phenyl)-propanol

30 To a solution, stirred at 0°C, of 12.3 ml of benzyl mercaptan in 100 ml of tetrahydrofuran there are added dropwise 49 ml of a 1.6 M solution of butyllithium in hexane and after a further 15 minutes' stirring at 0°C. a solution of 12.1 g of 3-



[2(R)-isopropyl-3-(3-acetoxy-4-tert-butyl-phenyl)-propanoyl]-  
4(R)-benzyl-oxazolidin-2-one in 100 ml of tetrahydrofuran. The  
reaction solution is stirred at 0°C for a further 90 minutes and  
is then added dropwise at 0°C, with stirring, to a suspension of  
5 4.9 g of LiAlH<sub>4</sub> in 100 ml of tetrahydrofuran. The reaction  
mixture is stirred for a further 150 minutes at 0°C and then, in  
succession, 26.8 ml of ethyl acetate, 100 ml of  
tetrahydrofuran/water=1:1 and 400 ml of 2N H<sub>2</sub> SO<sub>4</sub> are added  
dropwise thereto. The tetrahydrofuran is removed using a rotary  
10 evaporator and the suspension that remains is partitioned  
between diethyl ether and water. The organic phases are  
concentrated by evaporation and the residue is purified by FC  
(300 g of silica gel, dichloromethane/ethyl acetate=9:1 and 200  
g of silica gel, ethyl acetate/hexane=1:2), yielding the title  
15 compound: R<sub>f</sub> (ethyl acetate/hexane=1:2)=0.43.

k) 3-[2(R)-Isopropyl-3-(3-acetoxy-4-tert-butyl-phenyl)-  
propanoyl]-4(R)-benzyl-oxazolidin-2-one

20 Analogously to Example 1e), the title compound is obtained  
starting from 3-acetoxy-4-tert-butyl-benzyl bromide and by  
purification using FC (silica gel, dichloromethane/hexane=7:3):  
R<sub>f</sub> (dichloromethane/hexane=8:2)=0.29.

25 1) 3-Acetoxy-4-tert-butyl-benzyl bromide

16.4 g of N-bromosuccinimide, 1 g of α,α'-  
azoisobutyronitrile and 1 g of dibenzoyl peroxide are added in  
succession to a solution, stirred at 70°C, of 19 g of 3-acetoxy-  
30 4-tert-butyltoluene in 900 ml of CCl<sub>4</sub>. The reaction mixture is  
stirred under reflux for 31/2 hours under UV irradiation and is  
filtered, and the filtrate is concentrated by evaporation. The  
title compound is obtained from the residue by means of FC (900

g of silica gel, hexane/ethyl acetate=95:5):  $R_f$  (hexane/ethyl acetate=95:5)=0.40.

**EXAMPLE 6**

5           2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(2-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide hydrochloride

          Analogously to Example 1, the title compound is prepared  
10 starting from 20 mg of N-tert-butoxycarbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(2-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide by removal of the N-tert-butyloxy-carbonyl group using 4 N hydrochloric acid in dioxane, and is purified by means of FC (8 g of silica gel,  
15 dichloromethane/methanol=9:1).  $R_f$  (dichloromethane/methanol=8:2)=0.50;  $R_t$  (I) 28.47, 28.99 minutes; FAB-MS  $(M+H)^+ = 435$ .

          The starting materials are prepared as follows:

20

          a) N-Tert-butoxycarbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(2-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide.

25

          The title compound is prepared analogously to Example 5a) starting from N-tert-butoxy-carbonyl-2-methylene-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(2-benzyloxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide and is purified by means of FC (silica gel, hexane/ethyl acetate=2:1, ethyl acetate):

30

$R_f$  (hexane/ethyl acetate=1:1)=0.36.

That starting material is obtained analogously to Example 5, the 2-benzyloxy-4-tert-butyl-benzyl bromide to be used in step k) being prepared as follows:

5           1) 2-Benzyloxy-4-tert-butyl-benzyl bromide

2.9 ml of trimethylsilyl bromide are added to a solution, stirred at room temperature, of 4 g of 2-benzyloxy-4-tert-butyl-benzyl alcohol in 100 ml of chloroform. The reaction mixture is  
10 stirred for a further 1 hour and then partitioned between trichloromethane and water. The organic phases are dried with  $\text{Na}_2\text{SO}_4$  and concentrated by evaporation, yielding the title compound:  $R_f$  (dichloromethane/hexane=8:2)=0.95.

15           m) 2-Benzyloxy-4-tert-butyl-benzyl alcohol

A solution of 6.44 g of 2-benzyloxy-4-tert-butylbenzoic acid benzyl ester in 10 ml of tetrahydrofuran is slowly added dropwise to a suspension, stirred at room temperature, of 0.47 g  
20 of  $\text{LiAlH}_4$  in 40 ml of tetrahydrofuran. The reaction mixture is stirred for a further 4 hours at room temperature and then, in succession, 0.96 ml of ethyl acetate, 6.4 ml of tetrahydrofuran/water=1:1 and 9.6 ml of 2 N  $\text{H}_2\text{SO}_4$  are added dropwise thereto. The suspension is partitioned between ethyl  
25 acetate and water/saturated sodium chloride solution, the organic phases are concentrated by evaporation and the residue is purified by means of FC (150 g of silica gel, dichloromethane/hexane=6:4). Title compound:  $R_f$  (dichloromethane/hexane=8:2)=0.24.

30

n) 2-Benzyloxy-4-tert-butyl-benzoic acid benzyl ester

A mixture of 5 g of 2-hydroxy-4-tert-butyl-benzoic acid, 9.1 ml of benzyl bromide, 17 g of caesium carbonate, 0.3 g of sodium iodide and 500 ml of acetone is stirred for 20 hours under reflux and then filtered and the filtrate is concentrated by evaporation. The residue is partitioned between diethyl ether and water, the organic phases are concentrated by evaporation and the residue is purified by means of FC (1000 g of silica gel, dichloromethane/hexane=1:1). Title compound:  $R_f$  (dichloromethane/hexane=1:1)=0.47.

#### EXAMPLE 7

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-ethoxycarbonylmethoxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 62 mg of N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-ethoxycarbonylmethoxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide and is purified by means of FC (20 g of silica gel, dichloromethane/methanol=9:1). This yields the title compound:  $R_f$  (dichloromethane/methanol=9:1)=0.33;  $R_t$  (I)=34.5 and 34.8 minutes; FAB-MS  $(M+H)^+ = 521$ .

The starting materials are obtained as follows:

a) N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-ethoxycarbonylmethoxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide

A mixture of 52 mg of N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide (Example 5a), 47.5 mg

of caesium carbonate, 0.012 ml of iodoacetic acid ethyl ester and 5 ml of acetone is stirred for 3 hours under reflux and then concentrated by evaporation. The residue is partitioned between diethyl ether and water. The organic phases are dried and  
5 combined and then concentrated by evaporation, yielding the title compound in the form of the crude product:  $R_f$  (dichloromethane/diethyl ether=8:2)=0.28.

**EXAMPLE 8**

10 2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-allyloxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared  
15 starting from 45 mg of N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-allyloxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide and is purified by FC (20 g of silica gel, dichloromethane/methanol=9:1). This yields the title compound:  $R_f$  (dichloromethane/methanol=9:1)=0.20; FAB-MS  
20  $(M+H)^+ = 475$ .

The starting material is prepared analogously to Example 7a) using allyl iodide.

**EXAMPLE 9**

25 2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-methoxycarbonylallyloxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide hydrochloride

30 Analogously to Example 1, the title compound is prepared starting from 100 mg of N-tert-butoxy-carbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-methoxycarbonylallyloxy-4-tert-butyl-phenyl)-octanoic acid (N-

butyl)amide. This yields the title compound in the form of a diastereoisomeric mixture:  $R_f$

(dichloromethane/methanol=9:1)=0.36;  $R_t$  (I)=25.32 and 25.8 minutes; FAB-MS  $(M+H)^+ = 533$ .

5

The starting material is prepared analogously to Example 7a) using N-tert-butoxycarbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide and 4-bromo-2-butenic acid methyl ester.

10

#### EXAMPLE 10

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-methoxy-carbonylmethoxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide hydrochloride

15

Analogously to Example 1, the title compound is prepared starting from 91 mg of N-tert-butoxy-carbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-methoxy-carbonylmethoxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide and is purified by FC (15 g of silica gel, ethyl acetate/methanol=8:2). This yields the title compound in the form of a diastereoisomeric mixture:  $R_f$  (ethyl acetate/methanol=8:2)=0.45;  $R_t$  (I)=32.5 and 33.0 minutes; FAB-MS  $(M+H)^+ = 507$ .

25

The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide and bromoacetic acid methyl ester.

30

**EXAMPLE 11**

2 (R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-carbamoyl-methoxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide

5

Analogously to Example 1, the title compound is prepared starting from 59 mg of N-tert-butoxy-carbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-carboxamidomethoxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide and is  
10 purified by FC (20 g of silica gel, dichloromethane/methanol/conc. ammonia=140:10:1). This yields the title compound in the form of a diastereoisomeric mixture:  $R_f$  (dichloromethane/methanol/conc. ammonia=140:10:1)=0.23 and 0.32;  $R_t$  (I)=25.08 and 25.59 minutes; FAB-MS (M+H)<sup>+</sup>=492.

15

The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide and iodoacetamide.

20

**EXAMPLE 12**

2 (R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-3-(pyrid-2-yl, methoxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide hydrochloride

25

Analogously to Example 1, the title compound is prepared starting from 40 mg of N-tert-butoxy-carbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(pyrid-2-ylmethoxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide.

30

This yields the title compound in the form of a diastereoisomeric mixture:  $R_f$  (dichloromethane/methanol=9:1)=0.32;  $R_t$  (I)=24.52 and 25.19 minutes; FAB-MS (M+H)<sup>+</sup>=526.

The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide and 2-picolyl chloride hydrochloride.

**EXAMPLE 13**

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(pyrid-4-yl-methoxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 46 mg of N-tert-butoxy-carbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(pyrid-4-yl-methoxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound in the form of a diastereoisomeric mixture:  $R_f$  (dichloromethane/methanol=9:1)=0.17;  $R_t$  (I)=20.27 and 20.62 minutes; FAB-MS  $(M+H)^+ = 526$ .

20

The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide and 4-picolyl chloride hydrochloride.

25

**EXAMPLE 14**

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(N-oxido-pyrid-2-yl-methoxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide hydrochloride

30

Analogously to Example 1, the title compound is prepared starting from 35 mg of N-tert-butoxy-carbonyl-2(R,S)-methyl-



4 (S)-hydroxy-5 (S)-amino-7 (S)-isopropyl-8-[3-(N-oxidopyrid-2-yl-methoxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound in the form of a diastereoisomeric mixture:  $R_f$  (dichloromethane/methanol =9:1)=0.14;  $R_t$  (I)=31.06 and 31.6 minutes; FAB-MS  $(M+H)^+ =542$ .

The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl-2 (R,S)-methyl-4 (S)-hydroxy-5 (S)-amino-7 (S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic acid N-(butyl)amide and 2-picoly l chloride N-oxide.

#### EXAMPLE 15

2 (R,S)-Methyl-4 (S)-hydroxy-5 (S)-amino-7 (S)-isopropyl-8-[3-(2-ethoxycarbonylallyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 30 mg of N-tert-butoxy-carbonyl-2 (R,S)-methyl-4 (S)-hydroxy-5 (S)-amino-7 (S)-isopropyl-8-[3-(2-ethoxycarbonylallyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound in the form of a diastereoisomeric mixture:  $R_f$  (dichloromethane/methanol=9:1)=0.28;  $R_t$  (I)=39.3 and 39.8 minutes FAB-MS  $(M+H)^+ =547$ .

The starting material is prepared analogously to Example 7a) using N-tert-butoxycarbonyl-2 (R,S)-methyl-4 (S)-hydroxy-5 (S)-amino-7 (S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide and bromomethylacrylic acid ethyl ester.

**EXAMPLE 16**

2 (R,S) -Methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3-  
(2-ethoxycarbonylpropyloxy) -4-tert-butyl-phenyl-octanoic acid  
(N-butyl)amide hydrochloride

5

Analogously to Example 1, the title compound is prepared  
starting from 9 mg of N-tert-butoxy-carbonyl-2 (R,S) -methyl-4 (S) -  
hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3- (2-ethoxycarbonyl-  
propyloxy) -4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide.

10 This yields the title compound in the form of a  
diastereoisomeric mixture:  $R_f$  (dichloromethane/methanol  
=9:1)=0.25;  $R_t$  (I)=38.5; 39.0; 39.6 and 40.2 minutes; FAB-MS  
(M+H)<sup>+</sup> =549.

15 The starting material is prepared by hydrogenating N-tert-  
butoxycarbonyl-2 (R,S) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -  
isopropyl -8- [3- (2-ethoxycarbonylallyloxy) -4-tert-butyl-phenyl]-  
octanoic acid (N-butyl)amide (Example 15) with Raney nickel in  
ethanol at room temperature and under 2 bar H<sub>2</sub> :  $R_f$  (ethyl  
20 acetate/hexane=1:2)=0.16.

**EXAMPLE 17**

2 (R,S) -Methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3-  
(methylthio-methoxy) -4-tert-butyl-phenyl]-octanoic acid (N-  
25 butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared  
starting from 10 mg of N-tert-butoxycarbonyl-2 (R,S) -methyl-4 (S) -  
hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3- (methylthio-methoxy) -4-  
30 tert-butyl-phenyl]-octanoic acid (N-butyl)amide. This yields the  
title compound in the form of a diastereoisomeric mixture:  $R_f$   
(dichloromethane/methanol=9:1)=0.2;  $R_t$  (I)=29.32 and 29.56  
minutes; FAB-MS (M+H)<sup>+</sup> =495.

The starting material is prepared as follows:

5 a) N-Tert-butoxycarbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-  
amino-7(S)-isopropyl-8-[3-(methylthio-methoxy)-4-tert-butyl-  
phenyl]-octanoic acid (N-butyl)amide

10 A solution of 100 mg of N-tert-butoxycarbonyl-2(R,S)-  
methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-  
tert-butyl-phenyl)-octanoic acid (N-butyl)amide (Example 5a) in  
5 ml of dimethylformamide is added dropwise to a suspension,  
stirred at room temperature, of 7.6 mg of a 65% NaH dispersion  
in 3 ml of dimethylformamide. The reaction mixture is stirred  
for a further 30 minutes at room temperature and then a solution  
15 of 0.017 ml of chlorodimethyl sulfide in 2 ml of  
dimethylformamide is added thereto. The reaction mixture is  
stirred for a further 24 hours and then concentrated by  
evaporation. The residue is partitioned between ether and water.  
The organic phases are concentrated by evaporation and the title  
20 compound is obtained from the residue by FC (12 g of silica gel,  
dichloromethane/diethyl ether=2:1):  $R_f$  (dichloromethane/diethyl  
ether=2:1)=0.33.

#### EXAMPLE 18

25 2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7-(S)-isopropyl-8-[3-  
(methyl-sulfonyl-methoxy)-4-tert-butyl-phenyl]-octanoic acid (N-  
butyl)amide hydrochloride

30 Analogously to Example 1, the title compound is prepared  
starting from 15 mg of N-tert-butoxy-carbonyl-2(R,S)-methyl-  
4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(methyl-sulfonyl-  
methoxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide. This  
yields the title compound in the form of a diastereoisomeric

mixture:  $R_f$  (dichloromethane/methanol=9:1)=0.75;  $R_t$  (I)=28.3 and 28.76 minutes; FAB-MS  $(M+H)^+ = 527$ .

The starting material is prepared as follows:

5

a) N-Tert-butoxycarbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(methylsulfonyl-methoxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide

10

With stirring at 0°C, a solution of 115 mg of potassium monopersulfate triple salt in 0.5 ml of water is added dropwise to a solution of 74 mg of N-tert-butoxycarbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(methylthio-methoxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide in

15

0.5 ml of methanol and the mixture is then stirred at room temperature for a further 20 hours. The reaction mixture is partitioned between dichloromethane and water. The organic phases are concentrated by evaporation and the title compound is obtained from the residue by FC (11 g of silica gel, ethyl

20

acetate/hexane=1:1):  $R_f$  (ethyl acetate/hexane=1:1)=0.26; FAB-MS  $(M+H)^+ = 627$ .

#### EXAMPLE 19

25

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(carboxy-methoxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide hydrochloride

30

Analogously to Example 1, the title compound is prepared starting from 28 mg of N-tert-butoxy-carbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(carboxy-methoxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound in the form of a diastereoisomeric mixture:  $R_f$

(dichloromethane/methanol=9:1)=0.26;  $R_t$  (I)=26.1 and 28.0 minutes; FAB-MS  $(M+H)^+ = 493$ .

The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-butyl-phenyl)-octanoic acid (N-butyl)amide and bromoacetic acid benzyl ester, with subsequent removal of the benzyl group by hydrolysis (Pd/C-ethanol).

#### EXAMPLE 20

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3,3-dimethyl-2-oxo-butyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 42 mg of N-tert-butoxy-carbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3,3-dimethyl-2-oxo-butyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide.

This yields the title compound in the form of a diastereoisomeric mixture:  $R_t$  (dichloromethane/methanol=9:1)=0.3;  $R_t$  (I)=37.3 and 37.8 minutes; FAB-MS  $(M+H)^+ = 533$ .

The starting material is prepared analogously to Example 17a) using N-tert-butoxy-carbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide and 1-bromopinacolone.

#### EXAMPLE 21

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2-nitrobenzyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 53 mg of N-tert-butoxy-carbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2-nitrobenzyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound in the form of a diastereoisomeric mixture:  $R_f$  (dichloromethane/methanol=9:1)=0.35;  $R_t$  (I)=52.0 and 52.4 minutes; FAB-MS(M+H)<sup>+</sup>=570.

The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-butyl-phenyl)-octanoic acid (N-butyl)amide and 2-nitrobenzyl chloride.

#### EXAMPLE 22

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2-amino-benzyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide hydrochloride

The title compound is prepared starting from 35 mg of 2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2-nitrobenzyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide (Example 21) by hydrogenation with Pt/C in tetrahydrofuran at room temperature and under normal pressure and is purified by FC (10 g of silica gel, dichloromethane/methanol=9:1). This yields the title compound in the form of a diastereoisomeric mixture:  $R_f$  (dichloromethane/methanol=9:1)=0.27;  $R_t$  (I)=30.5 and 31.3 minutes; FAB-MS(M+H)<sup>+</sup>=539.

**EXAMPLE 23**

2 (R,S) -Methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3-  
(3-chloro-2 (R,S) -hydroxy-propyloxy) -4-tert-butyl-phenyl] -  
octanoic acid (N-butyl)amide hydrochloride

5

Analogously to Example 1, the title compound is prepared  
starting from 31 mg of N-tert-butoxy-carbonyl-2 (R,S) -methyl-  
4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3- (2,3-  
epoxypropyloxy) -4-tert-butyl-phenyl] -octanoic acid (N-  
10 butyl)amide. This yields the title compound in the form of a  
diastereoisomeric mixture:  $R_f$   
(dichloromethane/methanol=9:1)=0.18;  $R_t$  (I)=31.9 and 32.3  
minutes; FAB-MS (M+H)<sup>+</sup> =527.

15

The starting material is prepared analogously to Example  
7a) using N-tert-butoxy-carbonyl-2 (R,S) -methyl-4 (S) -hydroxy-  
5 (S) -amino-7 (S) -isopropyl-8- (3-hydroxy-4-tert-butylphenyl) -  
octanoic acid (N-butyl)amide and epibromohydrin.

20 **EXAMPLE 24**

2 (R,S) -Methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3-  
(3-methylthio-2 (S,R) -hydroxypropyloxy) -4-tert-butyl-phenyl] -  
octanoic acid (N-butyl)amide hydrochloride

25

Analogously to Example 1, the title compound is prepared  
starting from 15 mg of N-tert-butoxy-carbonyl-2 (R,S) -methyl-  
4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3- (3-methylthio-  
2 (S,R) -hydroxypropyloxy) -4-tert-butyl-phenyl] -octanoic acid (N-  
butyl)amide. This yields the title compound in the form of a  
30 diastereoisomeric mixture:  $R_f$   
(dichloromethane/methanol=9:1)=0.32;  $R_t$  (I)=32.6 and 32.9  
minutes; FAB-MS (M+H)<sup>+</sup> =53

The starting material is prepared as follows:

a) N-tert-butoxycarbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-methylthio-2(S,R)-hydroxypropyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide

18 mg of sodium methanethiolate are added to a solution of 150 mg of N-tert-butoxycarbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2,3-epoxypropyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide in 10 ml of methanol and the mixture is maintained under reflux for 7 hours. The reaction mixture is concentrated by evaporation and the residue is partitioned between dichloromethane and water. The organic phases are concentrated by evaporation and the title compound is obtained from the residue after purification by means of FC (20 g of silica gel, dichloromethane/diethyl ether=1:1):  $R_f$  (dichloromethane/diethyl ether=1:1)=0.33; FAB-MS  $(M+H)^+ = 639$ .

#### EXAMPLE 25

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-methylsulfonyl-2(S,R)-hydroxypropyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 14 mg of N-tert-butoxy-carbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-methyl-sulfonyl-2(S,R)-hydroxypropyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound in the form of a diastereoisomeric mixture:  $R_f$  (dichloromethane/methanol=9:1)=0.16;  $R_t$  (I)=26.3 and 26.8 minutes; FAB-MS  $(M+H)^+ = 571$ .



The starting material is prepared analogously to Example 18a) using 62 mg of N-tert-butoxycarbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-methylthio-2(S,R)-hydroxypropyloxy)-4-tert-butyl-phenyl]-octanoic acid (N-butyl)amide:  $R_f$  (ethyl acetate)=0.60; FAB-MS  $(M+H)^+ = 671$ .

**EXAMPLE 26**

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(methylsulfonyl-methoxy)-4-tert-butyl-phenyl]-octanoic acid (N-3-morpholino-propyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 18 mg of N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-methylsulfonyl-methoxy)-4-tert-butyl-phenyl)-octanoic acid (N-3-morpholino-propyl)amide. This yields the title compound:  $R_f$  (dichloromethane/methanol=8:2)=0.16;  $R_t$  (I)=17.61 minutes; FAB-MS  $(M+H)^+ = 598$ .

The starting material is prepared analogously to Examples 17a) and 18a) using N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)octanoic acid (N-3-morpholino-propyl)amide and chlorodimethyl sulfide.

The N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-3-morpholino-propyl)amide is prepared analogously to Example 5a-1), except that in step 5b) or 1b) methacrylic acid (N-3-morpholino-propyl)amide is used instead of methacrylic acid butylamide.

**EXAMPLE 27**

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-methoxycarbonylmethoxy-phenyl)-octanoic acid (N-butyl)amide hydrochloride

5

Analogously to Example 1, the title compound is prepared starting from 12 mg of N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-methoxycarbonyl-methoxy-phenyl)-octanoic acid (N-butyl)amide. This yields the title  
10 compound:  $R_f$  (dichloromethane/methanol=9:1)=0.18;  $R_t$  (I)=21.74 minutes; FAB-MS(M+H)<sup>+</sup> =451.

The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-  
15 amino-7(S)-isopropyl-8-(3-hydroxyphenyl)-octanoic acid (N-butyl)amide and bromoacetic acid methyl ester.

The N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxyphenyl)-octanoic acid (N-  
20 butyl)amide used as starting material is prepared analogously to Example 5a)-5l), except that in step k) instead of 3-acetoxy-4-tert-butyl-benzyl bromide there is used 3-benzyloxy-benzyl bromide, so that in step i) 2(R)-isopropyl-3-(3-benzyloxy-phenyl)-propanol,  $R_f$  (dichloromethane/hexane=1:1)=0.19, is  
25 obtained directly.

**EXAMPLE 28**

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(methoxycarbonylmethoxy)-4-methoxy-phenyl]-octanoic acid (N-  
30 butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 15 mg of N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-

hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(methoxy-carbonylmethoxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide.

This yields the title compound:  $R_f$

(dichloromethane/methanol=9:1)=0.16;  $R_t$  (I)=19.33 minutes; FAB-

5 MS  $(M+H)^+ = 481$ .

The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic  
10 acid (N-butyl)amide and bromoacetic acid methyl ester.

The N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide used as starting material is prepared as  
15 follows:

a1) N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-benzyloxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide  
20

3.5 g of N-tert-butoxycarbonyl-2-methylene-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-benzyloxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide are hydrogenated in 30 ml of absolute methanol in the presence of 20 mg of  $[Ru_2Cl_4((S)-Binap)_2].NEt_3$  at room temperature and 25 bar for 5 hours. The  
25 reaction mixture is filtered and the filtrate is concentrated by evaporation. The residue is purified by FC (200 g of silica gel, hexane/ethyl acetate=1:1). Title compound:  $R_f$  (hexane/ethyl acetate=1:1)=0.16; FAB-MS  $(M+H)^+ = 599$ .

a2) N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide  
30

4.7 g of N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-benzyloxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide are hydrogenated in 60 ml of methanol in the presence of 2.35 g of 10% Pd/C at room temperature and under normal pressure for 1 hour. Filtration of the reaction mixture and concentration of the filtrate by evaporation under a high vacuum yield the title compound:  $R_f$  (hexane/ethyl acetate =1:1)=0.15; FAB-MS  $(M+H)^+ = 509$ .

The N-tert-butoxycarbonyl-2-methylene-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-benzyloxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide used as starting material is prepared analogously to Example 1 b) to i), except that in step i) 3-benzyloxy-4-methoxy-benzyl bromide is used instead of p-tert-butyl benzyl bromide.

#### EXAMPLE 29

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(N-methylcarbamoylmethoxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 18 mg of N-tert-butoxy-carbonyl-2(R)-methoxy-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(N-methylcarbamoylmethoxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound:  $R_f$  (dichloromethane/methanol=9:1)=0.21;  $R_t$  (I)=15.54 minutes; FAB-MS  $(M+H)^+ = 480$ .

The starting material is prepared as follows:

A mixture of 29 mg of N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(methoxycarbonylmethoxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide (Example 32), 6 ml of dimethylformamide and 1 ml of methylamine is left to stand in a bomb tube at room temperature for 60 hours. Concentration by evaporation and FC (5 g of silica gel, dichloromethane/methanol=9:1) of the residue yield the title compound:  $R_f$  (dichloromethane/methanol=9:1)=0.55.

10 **EXAMPLE 30**

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-methyl-sulfonyl-propyloxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide hydrochloride

15 Analogously to Example 1, the title compound is prepared starting from 30 mg of N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-methylsulfonyl-propyloxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound:  $R_f$   
20 (dichloromethane/methanol=9:1)=0.29;  $R_t$  (I)=17.83 minutes; FAB-MS(M+H)<sup>+</sup>=529.

The starting material is prepared analogously to Examples 17a) and 18a) using N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-methoxy-phenyl)-octanoic acid (N-butyl)amide and 3-methylthiopropyl iodide with subsequent oxidation to the sulfone.

**EXAMPLE 31**

30 2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(methylsulfonyl-methoxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 100 mg of N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(methylsulfonyl-methoxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide. This yields the  
5 title compound:  $R_f$  (dichloromethane/methanol=8:2)=0.5;  $R_t$  (I)=18.0 minutes; FAB-MS(M+H)<sup>+</sup> =501.

The starting material is prepared analogously to Examples 17a) and 18a) using N-tert-butoxycarbonyl-2(R)-methyl-4(S)-  
10 hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide and chlorodimethyl sulfide with subsequent oxidation to the sulfone.

#### EXAMPLE 32

15 2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-methoxy-propyloxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared  
20 starting from 27 mg of N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-methoxy-propyloxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide and is purified by FC (2 g of silica gel, dichloromethane/methanol=95:5). This yields the title compound:  $R_f$  (dichloromethane-  
25 methanol=9:1)=0.15;  $R_t$  (I)=21.9 minutes; FAB-MS(M+H)<sup>+</sup> =481.

The starting material is prepared analogously to Example 17a) using N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic  
30 acid (N-butyl)amide and 3-methoxy-propyl iodide.

**EXAMPLE 33**

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2-methoxyethoxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide hydrochloride

5

Analogously to Example 1, the title compound is prepared starting from 68 mg of N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2-methoxyethoxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide. This yields the  
10 title compound:  $R_f$  (dichloromethane/methanol=9:1)=0.32;  $R_t$  (I)=19.84 minutes; FAB-MS(M+H)<sup>+</sup>=467.

The starting material is prepared analogously to Example 17a) using N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-  
15 amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide and 2-methoxy-ethyl iodide.

**EXAMPLE 34**

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-hydroxy-propyloxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide hydrochloride  
20

Analogously to Example 1, the title compound is prepared starting from 93 mg of N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-  
25 hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-hydroxy-propyloxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound:  $R_f$  (dichloromethane/methanol=9:1)=0.24;  $R_t$  (I)=16.13 minutes; FAB-MS(M+H)<sup>+</sup>=467.

30 The starting material is prepared analogously to Example 17a) using N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide and 3-iodopropanol.

**EXAMPLE 35**

2 (R) -Methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3-  
(carbamoyl-methoxy) -4-methoxy-phenyl] -octanoic acid (N-  
5 butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 39 mg of N-tert-butoxy-carbonyl-2 (R) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3- (carbamoyl-methoxy) -4-  
10 methoxy-phenyl] -octanoic acid (N-butyl)amide. This yields the title compound:  $R_f$  (dichloromethane/methanol=8:2)=0.38;  $R_t$  (I)=13.86 minutes; FAB-MS (M+H)<sup>+</sup> =466.

The starting material is prepared analogously to Example  
15 7a) using N-tert-butoxy-carbonyl-2 (R) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- (3-hydroxy-4-methoxy-phenyl) -octanoic acid (N-butyl)amide and iodoacetamide.

**EXAMPLE 36**

20 2 (R) -Methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- (3-cyanomethoxy-4-methoxy-phenyl) -octanoic acid (N-butyl)amide

1.5 ml of a mixture of trifluoroacetic acid/dichloromethane=1:3 are added at 0°C, with stirring, to a  
25 solution of 35 mg of N-tert-butoxycarbonyl-2 (R) -methyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- (3-cyanomethoxy-4-methoxy-phenyl) -octanoic acid (N-butyl) -amide in 1 ml of dichloromethane, and the mixture is stirred for a further 3 hours at 0°C and then concentrated by evaporation. The residue  
30 is purified by FC (5 g of silica gel, dichloromethane/methanol=9:1). This yields the title compound:  $R_f$  (dichloromethane/methanol=9:1)=0.19;  $R_t$  (I)=19.59 minutes; FAB-MS (M+H)<sup>+</sup> =448.



The starting material is prepared analogously to Example 7a) using N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide and iodoacetonitrile.

**EXAMPLE 37**

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(4-methoxybutoxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 24 mg of N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(4-methoxy-butoxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound:  $R_f$  (dichloromethane/methanol=9:1)=0.29;  $R_t$  (I)=22.51 minutes; FAB-MS(M+H)<sup>+</sup>=495.

The starting material is prepared analogously to Example 17a) using N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide and 4-methoxy-propyl iodide.

**EXAMPLE 38**

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2-ethoxy-ethoxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 24 mg of N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(2-ethoxy-ethoxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide. This yields the

title compound:  $R_f$  (dichloromethane/methanol=9:1)=0.26;  $R_t$  (I)=21.32 minutes; FAB-MS(M+H)<sup>+</sup> =481.

The starting material is prepared analogously to Example 17a) using N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide and 2-iododiethyl ether.

#### EXAMPLE 39

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-{3-[2-(2-methoxy-ethoxy)ethoxy]-4-methoxy-phenyl}-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 27 mg of N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-{3-[2-(2-methoxy-ethoxy)ethoxy]-4-methoxy-phenyl}-octanoic acid (N-butyl)amide. This yields the title compound:  $R_f$  (dichloromethane/methanol=1:1)=0.19;  $R_t$  (I)=18.93 minutes; FAB-MS(M+H)<sup>+</sup> =511.

The starting material is prepared analogously to Example 17a) using N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide and 1-iodo-2-(2-methoxy-ethoxy)-ethane.

#### EXAMPLE 40

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-pentyloxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 53 mg of N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-

hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-pentyloxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide. This yields the title compound:  $R_f$  (dichloromethane/methanol=9:1)=0.25;  $R_t$  (I)=32.01 minutes; FAB-MS(M+H)<sup>+</sup> =479.

5

The starting material is prepared analogously to Example 17a) using N-tert-butoxycarbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide and iodopentane.

10

**EXAMPLE 41**

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-benzyloxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide hydrochloride

15

Analogously to Example 1, the title compound is prepared starting from 100 mg of N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-benzyloxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide. This yields the title compound:  $R_f$  (dichloromethane/methanol=9:1)=0.31;  $R_t$  (I)=44.21 minutes; FAB-MS(M+H)<sup>+</sup> =499.

20

The starting material is prepared analogously to Example 17a) using N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide and benzyl bromide.

25

**EXAMPLE 42**

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-ethoxy-propyloxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide hydrochloride

30

Analogously to Example 1, the title compound is prepared starting from 113 mg of N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(3-ethoxypropyloxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide. This yields the  
5 title compound:  $R_f$  (dichloromethane/methanol=9:1)=0.30;  $R_t$  (I)=23.11 minutes; FAB-MS (M+H)<sup>+</sup> =495.

The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-  
10 amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide and 1-ethoxy-3-iodopropane.

#### EXAMPLE 43

2(R)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(pyrid-4-yl-methoxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide hydrochloride  
15

Analogously to Example 1, the title compound is prepared starting from 71 mg of N-tert-butoxycarbonyl-2(R)-methyl-4(S)-  
20 hydroxy-5(S)-amino-7(S)-isopropyl-8-[3-(pyrid-4-yl-methoxy)-4-methoxy-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound:  $R_f$  (dichloromethane/methanol=9:1)=0.19;  $R_t$  (I)=32.95 minutes; FAB-MS (M+H)<sup>+</sup> =500.

25 The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl-2(R)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)amide and 4-picolyl chloride.

#### 30 EXAMPLE 44

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(2-ethoxy-carbonylmethoxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 67 mg of N-tert-butoxy-carbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(2-ethoxy-carboxylmethoxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)-amide. This yields the title compound in the form of a diastereoisomeric mixture:  $R_f$  (dichloromethane/methanol=9:1)=0.19;  $R_t$  (I)=35.7 and 36.5 minutes; FAB-MS(M+H)<sup>+</sup> =521.

The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(2-hydroxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide (Example 6a) and iodoacetic acid ethyl ester.

#### EXAMPLE 45

2(R,S)-Methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(2-ethoxy-carbonyl-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 80 mg of N-tert-butoxy-carbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(2-ethoxy-carboxylmethoxy-4-tert-butyl-phenyl)-octanoic acid (N-butyl)amide. This yields the title compound in the form of a diastereoisomeric mixture:  $R_f$  (dichloromethane/methanol=9:1)=0.21;  $R_t$  (I)=27.8 and 28.39 minutes; FAB-MS(M+H)<sup>+</sup> =492.

The starting material is prepared analogously to Example 7a) using N-tert-butoxy-carbonyl-2(R,S)-methyl-4(S)-hydroxy-5(S)-amino-7(S)-isopropyl-8-(2-hydroxy-4-tert-butyl-phenyl)-

octanoic acid (N-butyl)amide (Example 6a) and iodoacetamide.

**EXAMPLE 46**

2 (R) -Méthyl-4 (S) -hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3- (3-  
5 methoxy-propyloxy) -4,5-ethylenedioxy-phenyl] -octanoic acid (N-  
butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared  
starting from 34 mg of N-tert-butoxycarbonyl-2 (R) -methyl-4 (S) -  
10 hydroxy-5 (S) -amino-7 (S) -isopropyl-8- [3- (3-methoxy-propyloxy) -  
4,5-ethylenedioxy-phenyl] -octanoic acid (N-butyl)amide. This  
yields the title compound:  $R_f$

(dichloromethane/methanol=9:1)=0.16;  $R_f$  (I)=21.83 minutes; FAB-  
MS (M+H)<sup>+</sup> =509.

15 The starting material is prepared analogously to Example  
17a) using N-tert-butoxy-carbonyl-2 (R) -methyl-4 (S) -hydroxy-5 (S) -  
amino-7 (S) -isopropyl-8- (3-hydroxy-4,5-ethylenedioxy-phenyl) -  
octanoic acid (N-butyl)amide and 3-methoxy-propyl iodide.

20 The N-tert-butoxycarbonyl-2 (R) -methyl-4 (S) -hydroxy-5 (S) -  
amino-7 (S) -isopropyl-8- (3-hydroxy-4,5-ethylenedioxy-phenyl) -  
octanoic acid (N-butyl)amide is prepared analogously to Example  
28, except that in step i) instead of 3-benzyloxy-4-methoxy-  
25 benzyl bromide there is used 3-benzyloxy-4,5-ethylenedioxy-  
benzyl bromide. That compound is prepared as follows:

a) 5-Hydroxy-1,4-benzodioxane-7-carboxylic acid ethyl ester

A solution of 0.2 ml of 1,2-dibromoethane in 4 ml of  
30 dimethylformamide is added dropwise, four times at 2 hour  
intervals, to a solution, stirred at 100°C, of 2 g of gallic  
acid ethyl ester and 6.5 g of caesium carbonate in 80 ml of  
dimethylformamide. After being stirred for a further 2 hours at

100°C the reaction mixture is concentrated by evaporation and the residue is partitioned between diethyl ether and water. The organic phases are dried over sodium sulfate and concentrated by evaporation. The title compound is obtained from the residue by  
5 FC (50 g of silica gel, methylene chloride-methanol=8:2):  $R_f$  (methylene chloride/methanol=8:2)=0.39.

b) 5-Benzyloxy-1,4-benzodioxane-7-carboxylic acid ethyl ester

10 The reaction mixture containing 900 ml of acetone, 17.4 g of hydroxy-1,4-benzodioxane-7-carboxylic acid ethyl ester, 37.9 g of caesium carbonate, 11 ml of benzyl bromide and 7.7 g of sodium iodide is stirred under reflux for 3 hours and then concentrated by evaporation. The residue is partitioned between  
15 diethyl ether and water. The organic phases are dried over sodium sulfate and concentrated by evaporation. The title compound is obtained from the residue by FC (900 g of silica gel, hexane/ethyl acetate=1:1):  $R_f$  (hexane/ethyl acetate=2:1)=0.36.

20

c) 5-Benzyloxy-7-hydroxymethyl-1,4-benzodioxane

A solution of 1.28 g of 5-benzyloxy-1,4-benzodioxane-7-carboxylic acid ethyl ester in 5 ml of tetrahydrofuran is added dropwise at room temperature to a solution of 110 mg of lithium  
25 aluminium hydride in 10 ml of tetrahydrofuran and the mixture is stirred at room temperature for a further 30 minutes. Then 0.22 ml of ethyl acetate, 1.5 ml of a mixture (water/tetrahydrofuran=1:1) and finally 2.25 ml of 2 N sulfuric acid are added dropwise in succession. The reaction mixture is  
30 partitioned between diethyl ether and water. The organic phases are dried over sodium sulfate and concentrated by evaporation. The title compound is obtained from the residue by FC (240 g of

silica gel, ethyl acetate/hexane=1:2):  $R_f$  (ethyl acetate-hexane=1:2)=0.18.

d) 3-Benzylloxy-4,5-ethylenedioxy-benzyl bromide

5 0.07 ml of trimethylsilyl bromide is added to a solution of 0.1 g of 5-benzylloxy-7-hydroxymethyl-1,4-benzodioxane in 5 ml of chloroform and the mixture is stirred for a further 15 minutes at room temperature and then concentrated by evaporation in a rotary evaporator. The residue is immediately dissolved in a  
10 small amount of ethyl acetate; the same volume of hexane is added and the mixture is filtered through 15 g of silica gel, followed by elution with a mixture (hexane/ethyl acetate=4:1). Concentration of the eluates by evaporation yields the title compound:  $R_f$  (hexane/ethyl acetate=3:1)=0.48.

15 **EXAMPLE 47**

In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-(3-hydroxy-propyloxy)-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-2,2-dimethyl-ethyl)]-amide hydrochloride.

**EXAMPLE 48**

25 In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-isopropyl-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-2,2-dimethyl-ethyl)]-amide hydrochloride.

30 **EXAMPLE 49**

In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-tert-butyl-3-(3-methoxy -



propyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-2,2-dimethyl-ethyl)]amide hydrochloride.

**EXAMPLE 50**

5        In a manner analogous to that described in Examples 1 to 46 or 62 to 180, it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-(3-methyl-sulfonyl-propyloxy)-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-2-morpholinoethyl)amide dihydrochloride.

10

**EXAMPLE 51**

      In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-(3-methyl-sulfonyl-propyloxy)-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-2,2-dimethyl-ethyl)]-amide hydrochloride.

15

**EXAMPLE 52**

      In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[3,4-di(3-hydroxypropyloxy)phenyl]-octanoic acid (N-2-morpholinoethyl)amide dihydrochloride.

20

**EXAMPLE 53**

      In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[3,4-di(3-hydroxypropyloxy)phenyl]-octanoic acid [N-(2-carbamoyl-2,2-dimethyl-ethyl)]-amide hydrochloride.

30

**EXAMPLE 54**

In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-(3-N-methylcarbamoyl-propyl)-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-2-morpholinoethyl)amide dihydrochloride.

**EXAMPLE 55**

In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-(2-morpholinoethoxy)-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-2,2-dimethyl-ethyl)]-amide dihydrochloride.

**EXAMPLE 56**

In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[3-(3-methoxy-propyloxy)-4,5-ethylenedioxy-phenyl]-octanoic acid (N-2-morpholinoethyl)amide dihydrochloride.

**EXAMPLE 57**

In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[3-(3-methoxy-propyloxy)-4,5-ethylenedioxy-phenyl]-octanoic acid [N-(2-carbamoyl-2,2-dimethyl-ethyl)]-amide hydrochloride.

**EXAMPLE 58**

In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[3-(3-methoxy-propyloxy)-4,5-methylenedioxy-phenyl]-octanoic acid (N-2-morpholinoethyl)amide dihydrochloride.

**EXAMPLE 59**

In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[3-(3-methoxy-propyloxy)-4,5-methylenedioxy-phenyl]-octanoic acid [N-(2-carbamoyl-2,2-dimethylethyl)]-amide hydrochloride.

**EXAMPLE 60**

10 In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-2,2-ethylene-ethyl)]-amide hydrochloride.

15

**EXAMPLE 61**

In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(3(S)-2-oxo-pyrrolidin-3-yl-methyl)]amide hydrochloride.

20

**EXAMPLE 62**

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(4-methoxy-but-2-enoxy)-phenyl]-octanoic acid (N-butyl)-amide hydrochloride

25

Analogously to Example 1, the title compound is prepared starting from 66 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(4-methoxy-but-2-enoxy)-phenyl]-octanoic acid (N-butyl)-amide and is purified by FC (30 g of silica gel, dichloromethane/methanol=9:1). This yields the title compound:

30

R<sub>f</sub> (dichloromethane/methanol=9:1)=0.26; HPLC R<sub>t</sub> (I)=40.4 minutes; FAB-MS (M+H)<sup>+</sup> =493.

The starting material is prepared analogously to Example 17a) using 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-(3-hydroxy-4-methoxy-phenyl)-octanoic acid (N-butyl)-amide (Example 28) and 4-methoxy-but-2-enyl iodide.

#### 10 EXAMPLE 63

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-hydroxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide hydrochloride

15 Analogously to Example 1, the title compound is prepared starting from 20 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-hydroxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)-amide. This yields the title compound: R<sub>f</sub> (dichloromethane/methanol=9:1)=0.05; HPLC  
20 R<sub>t</sub> (I)=36.22 minutes; FAB-MS (M+H)<sup>+</sup> =467.

The starting material is prepared as follows:

a) 5(S)-Tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-hydroxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)-amide

1.34 g of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-benzyloxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)-amide are hydrogenated in the  
30 presence of 400 mg of 5% Pd/C in 50 ml of methanol for 10 minutes at room temperature and under normal pressure. The reaction mixture is filtered and concentrated by evaporation. The residue is purified by means of FC (50 g of silica gel,

hexane/ethyl acetate=1:1). The title compound is obtained:  $R_f$  (hexane/ethyl acetate=1:1)=0.16; HPLC  $R_t$  =17.42 minutes; FAB-MS:  $(M+H)^+ = 567$ .

5           The 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-benzyloxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)-amide used as starting material is prepared analogously to Example 28a1) and Examples 1b) to 1g), except that in step g) instead of 2(S)-isopropyl-3-(p-tert-butyl-phenyl)-propanol there is used 2(S)-isopropyl-3-[4-benzyloxy-3-(3-methoxypropyloxy)-phenyl]-propanol. That compound is prepared analogously to Example 124i) to m), except that in step m) instead of 4-methoxy-3-(3-methoxypropyloxy)-benzyl alcohol there is used 4-benzyloxy-3-(3-methoxypropyloxy)-benzyl  
10  
15 alcohol.

That compound is prepared as follows:

b) 4-Benzyloxy-3-(3-methoxypropyloxy)-benzaldehyde

20           A solution of 28.8 g of 4-benzyloxy-3-hydroxy-benzaldehyde in 100 ml of dimethyl-formamide is added dropwise to a suspension of 5.54 g of NaH (60% dispersion in mineral oil) in 150 ml of absolute dimethylformamide. The reaction mixture is stirred at room temperature. After 30 minutes, a solution of 29  
25 g of 3-methoxybromopropane in 120 ml of dimethylformamide is added thereto, and the mixture is stirred at room temperature for a further 4 hours and is then concentrated by evaporation under reduced pressure. The residue is partitioned between diethyl ether and water. The combined organic phases are dried  
30 over sodium sulfate and concentrated by evaporation, and the residue is purified by FC (100 g of silica gel, dichloromethane), yielding the title compound, which

crystallises spontaneously:  $R_f$  (dichloromethane/diethyl ether)=0.44.

c) 4-Benzyloxy-3-(3-methoxypropyloxy)-benzyl alcohol

5 A solution of 31 g of 4-benzyloxy-3-(3-methoxypropyloxy)-benzaldehyde in 530 ml of ethanol/water=8:2 is added dropwise to a suspension, stirred at 0°C, of 11.74 g of sodium boranate in 530 ml of a mixture of ethanol/water=8:2. The reaction mixture is stirred for one hour at 0°C and is then concentrated by  
10 evaporation. The residue is partitioned between diethyl ether and water. The combined organic phases are dried over sodium sulfate and concentrated by evaporation, and the residue is purified by FC (100 g of silica gel, dichloromethane/diethyl ether=1:1), yielding the title compound:  $R_f$   
15 (dichloromethane/diethyl ether=1:1)=0.43.

#### EXAMPLE 64

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-benzyloxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide hydrochloride  
20

Analogously to Example 1, the title compound is prepared starting from 60 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-benzyloxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide. This yields the  
25 title compound:  $R_f$  (dichloromethane/methanol=95:5)=0.08; HPLC  $R_t$  (I)=45.47 minutes; FAB-MS  $(M+H)^+ = 557$ .

#### EXAMPLE 65

30 5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[3,4-di(3-methoxypropyloxy)phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 66 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[3,4-di(3-methoxypropyloxy)phenyl]-octanoic acid (N-butyl)amide. This

5 yields the title compound:  $R_f$

(dichloromethane/methanol=9:1)=0.21;  $R_t$  (I)=40.0 minutes; FAB-MS  $(M+H)^+ = 539$ .

The starting material is prepared analogously to Example  
10 17a) using 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-hydroxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide and 3-methoxy-bromopropane.

#### EXAMPLE 66

15 5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(2,2,2-trifluoroethoxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared  
20 starting from 14 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(2,2,2-trifluoroethoxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound:  $R_f$   
(dichloromethane/methanol=9:1)=0.31; HPLC  $R_t$  (I)=28.7 minutes;  
25 FAB-MS  $(M+H)^+ = 549$ .

The starting material is prepared analogously to Example  
17a) using 5(S)-tert-butoxy-carbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-hydroxy-3-(3-methoxy-propyloxy)-  
30 phenyl]-octanoic acid (N-butyl)amide and 2,2,2-trifluoroethyl iodide.

#### EXAMPLE 67

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(3-hydroxypropyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide hydrochloride

5 Analogously to Example 1, the title compound is prepared starting from 20 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(3-hydroxy-propyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide and is purified by FC (2 g of silica gel,  
10 dichloromethane/methanol=9:1). This yields the title compound:  $R_f$  (dichloromethane/methanol=9:1)=0.09; HPLC  $R_t$  =11.03 minutes; FAB-MS (M+H)<sup>+</sup> =525.

The starting material is prepared analogously to Example  
15 17a) using 5(S)-tert-butoxy-carbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-hydroxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide and 3-iodopropanol.

#### EXAMPLE 68

20 5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(2-amino-ethoxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared  
25 starting from 7.5 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(2-amino-ethoxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound:  $R_f$  (dichloromethane/methanol/conc. ammonia=100:50:1)=0.28; HPLC  $R_t$  =6.77 minutes; FAB-MS (M+H)<sup>+</sup>  
30 =510.

The starting material is prepared analogously to Example  
17a) using 5(S)-tert-butoxy-carbonylamino-4(S)-hydroxy-7(S)-



isopropyl-2(R)-methyl-8-[4-hydroxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide and iodoacetonitrile, with subsequent reduction of the nitrile function to the amino group with Raney nickel/H<sub>2</sub> under normal pressure and at 40°C. in  
5 ethanol in the presence of 4% ammonia.

**EXAMPLE 69**

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(5-amino-pentyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid  
10 (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 22 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(5-amino-pentyloxy)-3-(3-methoxypropyloxy)-phenyl]octanoic acid (N-butyl)amide. This  
15 yields the title compound: R<sub>f</sub> (dichloromethane/methanol/conc. ammonia=100:50: 1)=0.11; HPLC R<sub>t</sub> =7.46 minutes; FAB-MS (M+H)<sup>+</sup> =552.

20 The starting material is prepared analogously to Example 17a) using 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-hydroxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide and 5-iodovaleric acid nitrile, with subsequent reduction of the nitrile function to  
25 the amino group with Raney nickel/H<sub>2</sub> under normal pressure and at 40°C in ethanol in the presence of 4% ammonia.

**EXAMPLE 70**

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-amino-butyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide hydrochloride  
30

Analogously to Example 1, the title compound is prepared starting from 36 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-amino-butyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide. This  
5 yields the title compound:  $R_f$  (dichloromethane/methanol/ammonia (conc.)=100:50:1)=0.15; HPLC  $R_t$  (I)=33.3 minutes; FAB-MS  $(M+H)^+$  =538.

The starting material is prepared analogously to Example  
10 17a) using 5(S)-tert-butoxy-carbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-hydroxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide and 4-iodobutyronitrile, with subsequent reduction of the nitrile function to the amino group with Raney nickel/ $H_2$  under normal pressure and at 40°C in  
15 ethanol in the presence of 4% ammonia, to form 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-amino-butyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide,  $R_f$  (dichloro-methane/methanol/conc. ammonia=100:50:1)=0.15, HPLC  $R_t$  =13.55 minutes.

20

**EXAMPLE 71**

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-N,N-dimethylamino-butyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide hydrochloride

25

Analogously to Example 1, the title compound is prepared starting from 30 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-N,N-dimethylamino-butyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound:  $R_f$   
30 (dichloromethane/methanol/ammonia (conc.)=100:50:1)=0.21; HPLC  $R_t$  =9.7 minutes; FAB-MS  $(M+H)^+$  =566.

The starting material is prepared by hydrogenation of 80 mg of 5(S)-tert-butoxycarbonyl-amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-amino-butyloxy)-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide (Example 70), dissolved in 5 6 ml of methanol and in the presence of 25 ml of 35% formaldehyde solution, with 30 mg of 10% Pd/C for a period of 19 hours at room temperature and under normal pressure, and is purified by FC (5 g of silica gel, dichloromethane/methanol/ammonia (conc.)=350:50: 1).  $R_f$  (dichloromethane/methanol/conc. ammonia=350:50:1)=0.21; HPLC  $R_t$  =14.18 minutes; FAB-MS  $(M+H)^+$  =666.

**EXAMPLE 72**

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-{4-[4-N-(trifluoromethanesulfonylaminobutyloxy)-3-(3-methoxypropyloxy)-phenyl]}-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 27 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-{4-[4-N-(trifluoromethanesulfonylaminobutyloxy)-3-(3-methoxypropyloxy)-phenyl]}-octanoic acid (N-butyl)amide. This yields the title compound:  $R_f$  (dichloromethane/methanol=9:1)=0.27; HPLC  $R_t$  =14.67 minutes; FAB-MS  $(M+H)^+$  =670.

The starting material is prepared as follows:

a) 5(S)-Tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-N-trifluoromethanesulfonylamido-butyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide

50 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-aminobutyloxy)-3-(3-

methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)-amide are dissolved in 4 ml of dichloromethane, and 23 ml of triethylamine and 13 ml of trifluoromethanesulfonic acid anhydride are added thereto at 0°C. The reaction mixture is stirred for 2 hours at  
5 room temperature and is then partitioned between dichloromethane (3x) and saturated NaHCO<sub>3</sub> solution (1x). The organic phases are combined, dried over magnesium sulfate and concentrated by evaporation. Purification of the residue by FC (15 g of silica gel, hexane/ethyl acetate=1:1) yields the title compound: R<sub>f</sub>  
10 (hexane/ethyl acetate=1:1)=0.26; HPLC R<sub>t</sub> =20.02 minutes.

**EXAMPLE 73**

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-carboxy-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide hydrochloride  
15

Analogously to Example 1, the title compound is prepared starting from 70 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-carboxy-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide. This  
20 yields the title compound: R<sub>f</sub> (dichloromethane/methanol=7:3)=0.35; HPLC R<sub>t</sub> (I)=37.18 minutes; FAB-MS (M+H)<sup>+</sup> =525.

25 The starting material is prepared analogously to Example 17a) using 5(S)-tert-butoxy-carbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-hydroxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide and bromoacetic acid benzyl ester, with subsequent debenzylation in ethanol with 10% Pd/C at  
30 room temperature and under normal pressure.

**EXAMPLE 74**

5 (S)-Amino-4 (S)-hydroxy-7 (S)-isopropyl-2 (R)-methyl-8-[4-(3-ethoxycarbonyl-propyloxy)-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)-amide hydrochloride

5 Analogously to Example 1, the title compound is prepared starting from 27 mg of 5 (S)-tert-butoxycarbonylamino-4 (S)-hydroxy-7 (S)-isopropyl-2 (R)-methyl-8-[4-(3-ethoxycarbonylpropyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound:  $R_f$   
10 (dichloromethane/methanol=9:1)=0.24; HPLC  $R_t$  =18.18 minutes; FAB-MS  $(M+H)^+ =581$ .

The starting material is prepared analogously to Example 17a) using 5 (S)-tert-butoxy-carbonylamino-4 (S)-hydroxy-7 (S)-  
15 isopropyl-2 (R)-methyl-8-[4-hydroxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide and 4-iodobutyric acid ethyl ester.

#### EXAMPLE 75

20 5 (S)-Amino-4 (S)-hydroxy-7 (S)-isopropyl-2 (R)-methyl-8-[4-(3-carboxypropyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared  
25 starting from 41 mg of 5 (S)-tert-butoxycarbonylamino-4 (S)-hydroxy-7 (S)-isopropyl-2 (R)-methyl-8-[4-(3-carboxypropyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound:  $R_f$   
(dichloromethane/methanol=9:1)=0.20; HPLC  $R_t$  (I)=37.65 minutes;  
30 FAB-MS  $(M+H)^+ =553$ .

The starting material is prepared from 5 (S)-tert-butoxycarbonylamino-4 (S)-hydroxy-7 (S)-isopropyl-2 (R)-methyl-8-

[4-(3-ethoxycarbonylpropyloxy)-3-(3-methoxypropyloxy)phenyl]-octanoic acid (N-butyl)amide (Example 74) by hydrolysis of the ester function in methanolic solution with 2 equivalents of 1N sodium hydroxide, by stirring for 24 hours at room temperature.

5 The reaction mixture is concentrated by evaporation, an aqueous solution of the residue acidified to pH 4 is extracted with ethyl acetate, and the product obtained therefrom is purified by FC (dichloromethane/methanol=9:1).  $R_f$  (dichloromethane/methanol=95:5)=0.41.

10

**EXAMPLE 76**

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-methoxy-carbonylbutyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide hydrochloride

15

Analogously to Example 1, the title compound is prepared starting from 29 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-methoxy-carbonylbutyloxy)-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound:  $R_f$  (dichloromethane/methanol=9:1)=0.24; HPLC  $R_t$  (I)=42.55 minutes; FAB-MS  $(M+H)^+ = 581$ .

20

The starting material is prepared analogously to Example 17a) using 5(S)-tert-butoxy-carbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-hydroxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide and 5-iodovaleric acid methyl ester.

25

30 **EXAMPLE 77**

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-carboxy-butyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 10 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-carboxy-butyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-butyl)amide. This yields the title compound:  $R_f$  (dichloromethane/methanol=8:2)=0.34; HPLC  $R_t$  =9.92 minutes; FAB-MS  $(M+H)^+ =567$ .

The starting material is prepared from 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-(4-methoxycarbonyl-butyloxy)-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid (N-butyl)amide (Example 76) by hydrolysis of the ester function in methanolic solution with 2 equivalents of 1 N sodium hydroxide, by stirring for 24 hours at room temperature. The reaction mixture is concentrated by evaporation, the residue is dissolved in water, and the solution is acidified to pH 4 and extracted with ethyl acetate. The organic phases are dried over magnesium sulfate and concentrated by evaporation. Purification of the residue by FC (silica gel, dichloromethane/methanol=9:1) yields the title compound:  $R_f$  (dichloromethane/methanol/conc. ammonia=350:50:1)=0.14.

#### EXAMPLE 78

In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(3(R)-2-oxo-pyrrolidin-3-yl-methyl)]-amide hydrochloride,

5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(3(S)-2-oxo-piperidin-3-yl-methyl)]-amide hydrochloride,

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-  
3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (3 (R) -2-oxo-  
piperidin-3-yl-methyl)] -amide hydrochloride,

5

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-  
3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (3-carbamoyl-  
3,3-dimethyl-propyl)] -amide hydrochloride,

10

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-  
3- (4-methoxy-butyl) -phenyl] -octanoic acid [N- (5 (S) -2-  
pyrrolidinon-5-yl-methyl)] -amide hydrochloride,

15

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-  
3- (4-methoxy-butyl) -phenyl] -octanoic acid [N- (5 (R) -2-  
pyrrolidinon-5-yl-methyl)] -amide hydrochloride,

20

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-  
3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (6 (S) -2-oxo-  
piperidin-6-yl-methyl)] -amide hydrochloride,

25

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-  
3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (6 (R) -2-oxo-  
piperidin-6-yl-methyl)] -amide hydrochloride,

25

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-  
3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (2-thiazol-2-  
yl-ethyl)] -amide dihydrochloride,

30

5 (S) -amino-4 (S) -hydroxy-2 (S) -7 (S) -diisopropyl-8- [4-methoxy-  
3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (4 (S) -2-  
oxazolidinon-4-yl-methyl)] -amide hydrochloride,



5 (S)-amino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(4 (R)-2-oxazolidinon-4-yl-methyl)]-amide hydrochloride,

5 5 (S)-amino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(3 (S)-2,5-dioxo-pyrrolidin-3-yl-methyl)]-amide hydrochloride,

10 5 (S)-amino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(3 (R)-2,5-dioxo-pyrrolidin-3-yl-methyl)]-amide hydrochloride,

15 5 (S)-amino-4 (S)-hydroxy-2 (S)-7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(2,6-dioxo-piperidin-4-yl-methyl)]-amide hydrochloride, or

20 5 (S)-amino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(4 (S)-2-oxothiazolidin-4-yl-methyl)]-amide hydrochloride.

#### EXAMPLE 79

In a manner analogous to that described in Examples 1 to 46 or 62 to 180 it is also possible to prepare

25 5 (S)-amino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[3-(3-methoxypropoxy)-4,5-ethylene-dioxy-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)-amide,

30 5 (S)-amino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxy-propyloxy)phenyl]-octanoic acid [N-(4 (R)-2-oxothiazolidin-4-yl-methyl)]-amide hydrochloride,

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (tetrahydro-2-pyrimidon-5-yl-methyl)] -amide hydrochloride,

5 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (N-acetyl-2-amino-2-methyl-propyl)] -amide hydrochloride,

10 5 (S) -amino-4 (S) -hydroxy-2 (S) -7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (N-formyl-2-amino-2-methyl-propyl)] -amide hydrochloride,

15 5 (S) -amino-4 (S) -hydroxy-2 (S) -7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (4-acetyl-piperazinyl-ethyl)] -amide hydrochloride,

20 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (2,4-imidazolinedion-5-yl-methyl)] -amide hydrochloride,

5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (4-methoxy-butyl) -phenyl] -octanoic acid [N- (2-hydroxy-pyridin-6-yl-methyl)] -amide hydrochloride,

25 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (2,2-dimethyl-2-sulfamoyl-ethyl)] -amide hydrochloride,

30 5 (S) -amino-4 (S) -hydroxy-2 (S) -7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (2,2-dimethyl-2- (N,N-dimethyl) -sulfamoyl-ethyl)] -amide hydrochloride,

5 (S) -amino-4 (S) -hydroxy-2 (S) -7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (2-oxo-piperidin-3 (R) -yl)] -amide hydrochloride,

5 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (2-oxo-piperidin-3 (S) -yl)] -amide hydrochloride,

10 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (2-oxo-piperidin-4-yl)] -amide hydrochloride,

15 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid [N- (N-acetyl-piperidin-4-yl)] -amide hydrochloride, or

20 5 (S) -amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (4-methoxy-but-1-enyl) -phenyl] -octanoic acid [N- (2-carbamoyl-2,2-dimethyl-ethyl)] -amide hydrochloride.

#### EXAMPLE 80

25 5 (S) -Amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxypropyloxy) -phenyl] -octanoic acid (N-butyl)amide hydrochloride

Analogously to Example 1, the title compound is prepared starting from 82 mg of 5 (S) -tert-butoxycarbonylamino-4 (S) -hydroxy-2 (S) -7 (S) -diisopropyl-8- [4- (4-methoxy-3- (3-methoxy-propyloxy) -phenyl] -octanoic acid (N-butyl)amide. This yields the title compound:  $R_f$  (dichloromethane/methanol=9:1)=0.32; HPLC  $R_t$  (I)=42.32 minutes; FAB-MS  $(M+H)^+ = 509$ .

The starting material is prepared analogously to Examples 206a) and 200b) from 3-tert-butoxycarbonyl-5(S)-[2(S)-carboxy-3-methyl-butyl]-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine  
5 (Example 200 c) and n-butylamine.

**EXAMPLE 81**

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(2-methoxymethoxyethyl)-phenyl]-octanoic acid (N-butyl)amide  
10

50 mg of 5(S)-azido-4(S)-hydroxy-8(R,S)-isobutyroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(2-methoxymethoxyethyl)-phenyl]-octanoic acid (N-butyl)amide are hydrogenated in 10 ml of methanol in the presence of 50 mg of 10% Pd/C at room  
15 temperature and under normal pressure. The reaction mixture is filtered and concentrated by evaporation. The residue is purified by means of FC (2 g of silica gel, dichloromethane/methanol=9:1). The title compound is obtained:  
R<sub>f</sub> (dichloromethane/methanol=9:1)=0.19; HPLC R<sub>t</sub> =13.42 minutes;  
20 FAB-MS (M+H)<sup>+</sup> =509.

The starting material is prepared as follows:

a) 2-(2-Hydroxyethyl)-anisole

25 To a solution of 10 g of 2-(2-hydroxyphenyl)-ethanol in 200 ml of acetone there are added 35.3 g of Cs<sub>2</sub>CO<sub>3</sub> and then a solution of 6.5 ml of methyl iodide in 40 ml of acetone. The reaction mixture is stirred for 50 minutes at room temperature, is filtered and is concentrated by evaporation. The residue is  
30 partitioned between diethyl ether and water. The organic phases are combined, dried over magnesium sulfate and concentrated by evaporation, and the residue is purified by means of FC (dichloromethane/diethyl ether=97:3), yielding the title

compound:  $R_f$  (dichloromethane/diethyl ether=97:3)=0.34; HPLC  $R_t$  =9.31 minutes.

b) 4-Bromo-2-(2-hydroxyethyl)-anisole

5        35.72 g of tetrabutylammonium tribromide am added in portions to a solution of 10.7 g of 2-(2-hydroxyethyl)-anisole in 195 ml of dichloromethane and 130 ml of methanol. The reaction mixture is stirred for 150 minutes at room temperature and is then concentrated by evaporation in a rotary evaporator.  
10      The residue is partitioned between diethyl ether and water. The organic phases are combined, dried over magnesium sulfate and concentrated by evaporation, and the residue is purified by means of FC (dichloromethane), yielding the title compound:  $R_f$  (dichloromethane)=0.26; HPLC  $R_t$  =13.04 minutes.

15

c) 4-Bromo-2-(2-methoxymethoxy-ethyl)-anisole

1.48 g of N-ethyl-diisopropylamine and 0.49 g of chlorodimethyl ether are added at room temperature to a solution of 948 mg of 4-bromo-2-(2-hydroxyethyl)-anisole in 30 ml of  
20      dichloromethane. The reaction mixture is stirred for 200 minutes at room temperature, and then 1 ml of water and 1 ml of 25% ammonium hydroxide solution are added thereto. The two-phase mixture is stirred vigorously for a further 15 minutes and then the organic phase is separated off, dried over sodium sulfate  
25      and concentrated by evaporation. Purification of the residue by means of FC (hexane/dichloromethane=1:1) yields the title compound:  $R_f$  (dichloromethane)=0.5; HPLC  $R_t$  =17.33 minutes.

d) 3(S)-Isopropyl-5(S)-{1(S)-azido-3(S)-isopropyl-4(R,S)-  
30      hydroxy-4-[4-methoxy-3-(2-methoxymethoxyethyl)-phenyl]-butyl}-tetrahydrofuran-2-one

Several iodine crystals am added to a suspension of 763 mg of magnesium chips in 0.5 ml of tetrahydrofuran, and the mixture

is activated in an ultrasound bath for 30 minutes. Then 4 drops of 1,2-dibromoethane and then a solution of 8.64 g of 4-bromo-2-(2-methoxymethoxyethyl)-anisole in 30 ml of tetrahydrofuran are added dropwise in such a manner that the reaction mixture boils under reflux. When the addition is complete, the mixture is maintained under reflux for a further one hour. The reaction mixture is then added dropwise within a period of 45 minutes, with stirring, to a solution, cooled to  $-75^{\circ}\text{C}$ , of 2.85 g of 3(S)-isopropyl-5(S)-[1(S)-azido-3(S)-isopropyl-4-oxobutyl]-tetrahydrofuran-2-one in 20 ml of tetrahydrofuran. The reaction mixture is stirred for a further 150 minutes at  $-75^{\circ}\text{C}$ , and there are then added thereto, at the same temperature, a solution of 1.4 ml of glacial acetic acid in 1 ml of tetrahydrofuran and then 25 ml of saturated ammonium chloride solution. The reaction mixture is then brought to room temperature, poured onto 60 ml of water and extracted three times with 100 ml of ethyl acetate. The organic phases are washed with 50 ml of saturated sodium chloride solution, combined, dried over magnesium sulfate and concentrated by evaporation. Purification of the residue by means of FC (400 g of silica gel, hexane/ethyl acetate=8:2) yields the title compound:  $R_f$  (hexane/ethyl acetate=7:3)=0.25; HPLC  $R_t$  =48.10 and 50.29 minutes (diastereoisomeric mixture).

e) 3(S)-Isopropyl-5(S)-{1(S)-azido-3(S)-isopropyl-4(R,S)-isobutyryloxy-4-[4-methoxy-3-(2-methoxymethoxyethyl)-phenyl]-butyl}-tetrahydrofuran-2-one

0.25 ml of pyridine, 0.31 ml of isobutyric acid anhydride and 15 mg of dimethylamino-pyridine are added to a solution of 300 mg of 3(S)-isopropyl-5(S)-{1(S)-azido-3(S)-isopropyl-4(R,S)-hydroxy-4-[4-methoxy-3-(2-methoxymethoxyethyl)-phenyl]-butyl}-tetrahydrofuran-2-one in 3.5 ml of dichloromethane, and the mixture is stirred for 80 hours at room temperature. The reaction mixture is then partitioned between dichloromethane

(3x), water (1x) and saturated sodium chloride solution (2x). The combined organic phases are dried over magnesium sulfate and concentrated by evaporation, and the residue is purified by FC (30 g of silica gel, hexane/ethyl acetate=8:2), yielding the  
5 title compound:  $R_f$  (hexane/ethyl acetate=8:2)=0.26; HPLC  $R_t$  =21.38 minutes and 21.76 minutes (diastereoisomeric mixture).

f) 5(S)-Azido-4(S)-hydroxy-2(S),7(S)-diisopropyl-8(R,S)-isobutyryloxy-8-[4-methoxy-3-(2-methoxymethoxyethyl)-phenyl]-  
10 octanoic acid (N-butyl)-amide

A solution of 170 mg of 3(S)-isopropyl-5(S)-{1(S)-azido-3(S)-isopropyl-4(R,S)-isobutyryloxy-4-[4-methoxy-3-(2-methoxymethoxyethyl)-phenyl]-butyl}-tetrahydrofuran-2-one in 1.4 ml of butylamine is stirred for 16 hours at room temperature and  
15 is then concentrated by evaporation. Purification of the residue by means of FC (hexane/ethyl acetate=7:3) yields the title compound:  $R_f$  (hexane/ethyl acetate=7:3)=0.25; HPLC  $R_t$  =20.38 and 20.8 minutes (diastereoisomeric mixture).

20 The 3(S)-isopropyl-5(S)-[1(S)-azido-3(S)-isopropyl-4-oxo-butyl]-tetrahydrofuran-2-one used in step d) is prepared as follows:

g) 2(S),7(S)-Diisopropyl-oct-4-ene-dicarboxylic acid [bis([4(S)-benzyl-oxazolidin-2-one])-amide

25 48 ml of a 1.0M solution of lithium hexamethyldisilazide in tetrahydrofuran are added dropwise, with stirring, at -75°C, within a period of one hour, to a solution of 11.5 g of 4(S)-benzyl-3-isovaleroyl-oxazolidin-2-one in 32 ml of tetrahydrofuran. The mixture is stirred further for 2 hours at -  
30 75°C and for 20 minutes at -20°C, and there are then added thereto 10 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidone (DMPU) and, within a period of 45 minutes, a solution of 4.28 g of 1,4-dibromo-2-butene in 10 ml of tetrahydrofuran.

The reaction mixture is stirred for a further 15 hours at -20°C and is then brought to 0°C within a period of one hour; 10 ml of saturated ammonium chloride solution are then added thereto at -20°C and, after 15 minutes, the mixture is brought to room

5 temperature. The reaction mixture is then partitioned between dichloromethane and saturated sodium chloride solution/water=1:1. The organic phases are combined, dried over sodium sulfate and concentrated by evaporation, and the residue is purified by means of FC (hexane/ethyl acetate=4:1), yielding  
10 the title compound:  $R_f$  (hexane/ethyl acetate=4:1)=0.30; HPLC  $R_t$  =21.6 minutes; FAB-MS  $(M+H)^+$  =575; m.p.=110°-111°C.  
(crystallised from ethyl acetate/hexane).

h) 3(S)-Isopropyl-5(S)-{1 (R)-bromo-4-methyl-3(S)-[(4(S)-benzyloxazolidin-2-one-3-yl)-carbonyl]-pentyl}-tetrahydrofuran-2-one  
15

10.5 g of N-bromosuccinimide are added, with stirring, to a solution of 30 g of 2(S),7(S)-diisopropyl-oct-4-ene-dicarboxylic acid [bis(4(S)-benzyl-oxazolidin-2-one)]-amide in 360 ml of  
20 tetrahydrofuran and 120 ml of water, the temperature being maintained at room temperature with an ice-bath. The reaction mixture is stirred for a further 2 hours at room temperature, and then the tetrahydrofuran is evaporated off in a rotary evaporator. The aqueous residue is partitioned between diethyl  
25 ether (2x200 ml), water (2x50 ml) and saturated sodium chloride solution (1x50 ml). The organic phases are combined, dried over magnesium sulfate and concentrated by evaporation, and the residue is purified by means of FC (90 g of silica gel, hexane/ethyl acetate=3:1), yielding the title compound in the  
30 form of a crude product. Crystallisation from diisopropyl ether yields the pure compound: m.p.=91°-92°C.;  $R_f$  (hexane/ethyl acetate=8:2)=0.28; HPLC  $R_t$  =19.53 minutes; FAB-MS  $(M+H)^+$  =494.



i) 3(S)-Isopropyl-5(S)-{1(S)-azido-4-methyl-3(S)-[(4(S)-benzyl-oxazolidin-2-on-3-yl)-carbonyl]-pentyl}-tetrahydrofuran-2-one

13.6 g of freshly dried tetrabutylammonium azide are added to a solution, stirred at room temperature, of 17.8 g of 3(S)-isopropyl-5(S)-{1(R)-bromo-4-methyl-3(S)-[(4(S)-benzyl-oxazolidin-2-on-3-yl)-carbonyl]-pentyl}-tetrahydrofuran-2-one in 180 ml of toluene, and a further 10 g of the azide are added in the course of 160 hours' stirring at room temperature. The reaction mixture is then partitioned between ethyl acetate and water (2x) and saturated sodium chloride solution (1x). The organic phases are combined, dried over sodium sulfate and concentrated. The title compound is obtained from the evaporation residue by means of FC (hexane/ethyl acetate=8:2) and crystallisation from diethyl ether/hexane: m.p.=102°-103°C.;  $R_f$  (hexane/ethyl acetate=8:2)=0.2; HPLC  $R_t$  =18.55 minutes; FAB-MS (M+H)<sup>+</sup> =457.

k) 3(S)-Isopropyl-5(S)-(1(S)-azido-3(S)-carboxy-4-methyl-pentyl)-tetrahydrofuran-2-one

175 ml of water, 74 ml of 30% hydrogen peroxide solution and 5.9 g of lithium hydroxide are slowly added in succession to a solution, stirred at -5°C, of 55.3 g of 3(S)-isopropyl-5(S)-{1(S)-azido-4-methyl-3(S)-[(4(S)-benzyl-oxazolidin-2-on-3-yl)-carbonyl]-pentyl}-tetrahydrofuran-2-one in 500 ml of tetrahydrofuran. The reaction mixture is stirred for one hour at 5°C and for 150 minutes at room temperature, and then 750 ml of aqueous 1M sodium sulfite solution are added at 3°C over a period of 30 minutes and the mixture is stirred for a further 30 minutes at room temperature. The reaction mixture is then freed of tetrahydrofuran by concentration, and the aqueous solution is washed three times with 1200 ml of ethyl acetate, the organic phases being back-extracted three times with 100 ml of 0.1 N

sodium hydroxide. The combined aqueous phases are adjusted to pH 1-2 with approximately 200 ml of 4N hydrochloric acid and are extracted with 3x1200 ml of ethyl acetate. The organic phases are combined, dried over magnesium sulfate and concentrated by evaporation, yielding the crude product which, for the purpose of cyclisation of the opened lactone, is dissolved in 500 ml of toluene and stirred for 2 hours at 50°C with approximately 1 g of molecular sieve and approximately 1 g of p-toluenesulfonic acid. Filtration, concentration by evaporation and purification of the residue by means of FC (hexane/ethyl acetate/glacial acetic acid=30:60:1) yield the title compound, which crystallises spontaneously: m.p.=56°-58°C.;  $R_f$  (hexane/ethyl acetate/glacial acetic acid=30:60:1)=0.62; HPLC  $R_t$  =14.46 minutes; FAB-MS  $(M+H)^+$  =298.

1) 3(S)-Isopropyl-5(S)-(1(S)-azido-3(S)-isopropyl-4-oxo-butyl)-tetrahydrofuran-2-one

1.45 ml of oxalyl chloride are added dropwise at 0°C, with stirring, within a period of 10 minutes, to a solution of 1.7 g of 3(S)-isopropyl-5(S)-(1(S)-azido-3(S)-carboxy-4-methyl-pentyl)-tetrahydrofuran-2-one in 20 ml of toluene. 0.03 ml of dimethylformamide is then added, and the temperature is then increased to 37°C within a period of 30 minutes. The reaction mixture is stirred for 2 hours at 37°C and is then clarified by filtration and concentrated by evaporation under reduced pressure at a bath temperature of 30°C. The residue is twice dissolved in 10 ml of toluene and concentrated by evaporation again in the same manner. The crude acid chloride so obtained is dissolved in 5 ml of tetrahydrofuran, and 16 ml of a 0.34 M solution of  $NaAlH(O\text{-}tert\text{-}bu)_3$  in diglyme (H. C. Brown et al., J. Org. Chem. (1992) 58.472) are added thereto at -75°C within a period of 30 minutes. The reaction mixture is stirred for 70 minutes at -75°C, and then a solution of 0.385 ml of glacial

acetic acid in 1 ml of tetrahydrofuran is added dropwise at the same temperature, followed by 2.1 ml of saturated  $\text{NH}_4\text{Cl}$  solution and then 20 ml of diethyl ether. The reaction mixture is brought to room temperature and is partitioned between diethyl ether and water/saturated sodium chloride solution. The organic phases are combined, dried over magnesium sulfate and concentrated by evaporation, and the residue is purified by means of FC (hexane/ethyl acetate=95:5), yielding the title compound:  $R_f$  (hexane/ethyl acetate=2:1)=0.55; HPLC  $R_t$  =16.41 minutes.

**EXAMPLE 82**

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-(3-hydroxypropyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-morpholinoethyl)amide hydrochloride

30 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-(3-hydroxypropyloxy)-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (N-2-morpholinoethyl)amide are dissolved in 1.5 ml of a 4 N solution, cooled to  $0^\circ\text{C}$ ., of hydrochloric acid in dioxane, and the mixture is then stirred for 10 minutes at  $0^\circ\text{C}$ . The reaction mixture is concentrated to dryness by evaporation under reduced pressure and at room temperature. Purification of the residue by means of FC (5 g of silica gel, dichloromethane/methanol=98:2) yields the title compound:  $R_f$  (dichloromethane/methanol=8:2)=0.20;  $R_t$  =10.43 minutes; FAB-MS  $(\text{M}+\text{H})^+$  =610.

The starting material is prepared as follows:

a) 2-(3-Methoxypropyloxy)-phenol

A solution of 22 g of pyrocatechol in 80 ml of dimethylformamide is added at room temperature, within a period

of 30 minutes, to a suspension of 8.4 g of NaH (60% dispersion in mineral oil) in 300 ml of dimethylformamide, and the mixture is stirred for one hour at room temperature. A solution of 49.3 g of 3-bromopropyl methyl ether in 80 ml of dimethylformamide is then added dropwise. The reaction mixture is stirred for a further 80 hours at room temperature and is then concentrated by evaporation under reduced pressure at a bath temperature of 30°C. The residue is partitioned between diethyl ether and water. The combined organic phases are dried over magnesium sulfate and concentrated by evaporation, and the residue is purified by FC (100 g of silica gel, hexane/dichloromethane=5:95), yielding the title compound:  $R_f$  (dichloromethane/diethyl ether=96:4)=0.35; HPLC  $R_t$  =11.2 minutes.

b) 4-Bromo-2-(3-methoxypropyloxy)-phenol

6.9 g of tetrabutylammonium tribromide are added in portions, at room temperature, to a solution of 2.6 g of 2-(3-methoxypropyloxy)-phenol in 60 ml of dichloromethane and 40 ml of methanol, and the mixture is then stirred for 30 minutes. The reaction mixture is concentrated by evaporation and the residue is partitioned between diethyl ether and water. The combined organic phases are dried over magnesium sulfate and concentrated by evaporation, and the residue is purified by FC (700 g of silica gel, dichloromethane/diethyl ether=98:2), yielding the title compound:  $R_f$  (dichloromethane/diethyl ether=97:3)=0.50; HPLC  $R_t$  =14.32 minutes; FAB-MS  $(M+H)^+$  =262.

c) 4-(3-Benzoyloxypropyloxy)-3-(3-methoxypropyloxy)-bromobenzene

A mixture of 4 g of 4-bromo-2-(3-methoxypropyloxy)-phenol, 2.3 g of potassium carbonate, 3.8 g of benzyl (3-bromopropyl) ether, a spatula tip of NaI and 15 ml of acetonitrile is stirred

under reflux for 30 hours. The reaction mixture is filtered and the filtrate is concentrated by evaporation. The residue is partitioned between ethyl acetate and water. The organic phases are combined, dried over magnesium sulfate and concentrated by evaporation, and the residue is purified by means of FC (hexane/ethyl acetate=95:5), yielding the title compound:  $R_f$  (hexane/ethyl acetate=9:1)=0.15; HPLC  $R_t$  =20.66 minutes.

d) 3(S)-Isopropyl-5(S)-{1(S)-azido-3(S)-isopropyl-4(R,S)-hydroxy-4-[4-(3-benzyloxy-propyloxy)-3-(3-methoxypropyloxy)-phenyl]-butyl}-tetrahydrofuran-2-one

1.3 ml of a 0.9M solution of butyllithium in hexane are slowly added dropwise to a solution, stirred at  $-75^{\circ}\text{C}$ , of 500 mg of 4-(3-benzyloxypropyloxy)-3-(3-methoxypropyloxy)-bromobenzene in 2 ml of tetrahydrofuran. The reaction mixture is stirred for 20 minutes at  $-75^{\circ}\text{C}$ , and then a suspension of magnesium bromide, freshly prepared from 44.5 mg of magnesium powder and 0.158 ml of 1,2-dibromoethane in 3 ml of tetrahydrofuran at room temperature, is added dropwise. The reaction mixture is stirred for a further 30 minutes at  $-75^{\circ}\text{C}$ , and then a solution of 172 mg of 3(S)-isopropyl-5(S)-[1(S)-azido-3(S)-isopropyl-4-oxo-butyl]-tetrahydrofuran-2-one in 2 ml of tetrahydrofuran is added dropwise. The mixture is again stirred for 30 minutes at  $-75^{\circ}\text{C}$ , and then 1.2 ml of saturated ammonium chloride solution are added dropwise at the same temperature. The reaction mixture is brought to room temperature and is then extracted three times with ethyl acetate. The organic phases are washed with water (2x) and saturated sodium chloride solution (1x), dried over magnesium sulfate, combined and concentrated by evaporation, and the residue is purified by means of FC (2x30 g of silica gel, hexane/ethyl acetate=6:2), yielding the title compound:  $R_f$  (hexane/ethyl acetate=2:1)=0.23; HPLC  $R_t$  =20.27 and 21.07 minutes (diastereoisomeric mixture); FAB-MS  $M^+$  =611.

e) 3(S)-Isopropyl-5(S)-{1(S)-azido-3(S)-isopropyl-4(R,S)-acetoxy-4-[4-(3-benzyloxy-propyloxy)-3-(3-methoxypropyloxy)-phenyl]-butyl}-tetrahydrofuran-2-one

5 A solution of 144 mg of 3(S)-isopropyl-5(S)-{1(S)-azido-3(S)-isopropyl-4(R,S)-hydroxy-4-[4-(3-benzyloxypropyloxy)-3-(3-methoxypropyloxy)-phenyl]-butyl}-tetrahydrofuran-2-one in 1.8 ml of acetic anhydride and 0.057 ml of pyridine is stirred for 30 hours at room temperature and is then concentrated to dryness by  
10 evaporation at room temperature and under reduced pressure. The residue is partitioned between dichloromethane (3x) and water/saturated sodium chloride solution (3x). The organic phases are combined, dried over magnesium sulfate and concentrated by evaporation, and the residue is purified by  
15 means of FC (hexane/ethyl acetate=4:1), yielding the title compound:  $R_f$  (hexane/ethyl acetate=2:1)=0.38 and 0.33; HPLC  $R_t$  =21.76 and 21.82 minutes (diastereoisomeric mixture); FAB-MS  $M^+$  =653,  $(M+Na)^+$  =676.

20 f) 3(S)-Isopropyl-5(S)-{1(S)-amino-3(S)-isopropyl-4-[4-(3-hydroxypropyloxy)-3-(3-methoxypropyloxy)-phenyl]-butyl}-tetrahydrofuran-2-one

A solution of 151 mg of 3(S)-isopropyl-5(S)-{1(S)-azido-3(S)-isopropyl-4(R,S)-acetoxy-4-[4-(3-benzyloxypropyloxy)-3-(3-methoxypropyloxy)-phenyl]-butyl}-tetrahydrofuran-2-one in 10 ml  
25 of ethanol is hydrogenated under normal pressure and at room temperature in the presence of 70 mg of PdO for 170 hours. The reaction mixture is filtered and concentrated by evaporation, and the residue is dissolved in 10 ml of ethanol and is again  
30 hydrogenated for 24 hours in the presence of 140 mg of PdO under normal pressure and at room temperature. Filtration and concentration by evaporation yield the title compound in the form of a crude product:  $R_f$  (dichloromethane/methanol)=0.32;

HPLC  $R_t$  =11.72 minutes; FAB-MS  $(M+H)^+$  =480. The compound is used in the next step without being purified.

g) 3(S)-Isopropyl-5(S)-{1(S)-tert-butoxycarbonylamino-3(S)-  
5 isopropyl-4-[4-(3-hydroxy-propyloxy)-3-(3-methoxypropyloxy)-  
phenyl]-butyl}-tetrahydrofuran-2-one

To a solution, stirred at 0°C, of 106 mg of 3(S)-isopropyl-  
5(S)-{1(S)-amino-3(S)-isopropyl-4-[4-(3-hydroxy-propyloxy)-3-(3-  
methoxypropyloxy)-phenyl]-butyl}-tetrahydrofuran-2-one in 4.5 ml  
10 of dichloromethane there are added dropwise a solution of 0.07  
ml of N-ethyldiisopropylamine in 0.1 ml of dichloromethane and  
then a solution of 77 mg of di-tert-butyl dicarbonate in 0.4 ml  
of dichloromethane. The reaction mixture is then brought to room  
temperature, is stirred at room temperature for 20 hours and is  
15 then concentrated to dryness by evaporation. Purification of the  
residue by means of FC (50 g of silica gel,  
dichloromethane/methanol=98:2) yields the title compound:  $R_f$   
(dichloromethane/methanol=95:5)=0.34; HPLC  $R_t$  =19.07 minutes;  
FAB-MS  $M^+$  =579,  $(M+Na)^+$  =602.

h) 5(S)-Tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-  
diisopropyl-8-[4-(3-hydroxypropyloxy)-3-(3-methoxypropyloxy)-  
phenyl]-octanoic acid (N-2-morpholinoethyl)amide

A mixture of 84 mg of 3(S)-isopropyl-5(S)-{1(S)-tert-  
25 butoxycarbonylamino-3(S)-isopropyl-4-[4-(3-hydroxypropyloxy)-3-  
(3-methoxypropyloxy)-phenyl]-butyl}-tetrahydrofuran-2-one, 0.6  
ml of 4-(2-aminoethyl)-morpholine and 0.025 ml of glacial acetic  
acid is stirred for 16 hours at room temperature and for 6 hours  
at 45°C and is then partitioned between diethyl ether (2x) and  
30 saturated  $NaHCO_3$  solution (ix) and water (2x). The organic  
phases are combined, dried over magnesium sulfate and  
concentrated by evaporation, and the residue is purified by  
means of FC (5 g of silica gel, dichloromethane/methanol=98:2),

yielding the title compound:  $R_f$

(dichloromethane/methanol=95:5)=0.16; HPLC  $R_t$  =14.49 minutes;

FAB-MS  $(M+H)^+ = 710$ .

5 **EXAMPLE 83**

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)-amide semifumarate

10 20 g of ice and 12 ml of 2 N NaOH are added in succession to a stirred solution of 2.35 g of 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)-amide hydrochloride (Example 137) in 20 ml of water, and the mixture  
15 is then extracted with 3x50 ml of tert-butyl methyl ether. The combined organic phases are dried with magnesium sulfate and concentrated by evaporation. 0.232 g of fumaric acid is added to the evaporation residue in 25 ml of methanol. The mixture is stirred until a clear solution has formed and is then  
20 concentrated by evaporation. The residue is crystallised from 100 ml of acetonitrile/ethanol=95:5. The crystals are filtered off with suction and dried at 60°C. The title compound is obtained in the form of a white powder having a melting point of 95°-104°C.

25

**EXAMPLE 84**

5(S)-Amino-2(S),7(S)-diisopropyl-4(S)-hydroxy-8-[4-tert-butyl-3-(3-methoxypropoxy)-phenyl]-octanoic acid [N-2-(morpholin-4-yl)-ethyl]-amide dihydrochloride

30

A 4N hydrochloric acid solution in dioxane (20 ml) is added at 0°-5°C to 768 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-tert-butyl-3-(3-



methoxypropoxy)-phenyl]-octanoic acid [N-2-(morpholin-4-yl)-ethyl]-amide, and the mixture is then stirred for one hour. The solvent is then removed by lyophilisation under a high vacuum, the residue is dissolved in anhydrous dichloromethane and  
5 filtered over cotton wool, and the filtrate is concentrated. A small amount of 4N hydrochloric acid in dioxane is again added to the residue, the resulting solution is lyophilised, and the residue is dried under a high vacuum. The title compound is obtained in the form of a white amorphous solid:  $R_f$   
10 (dichloromethane/methanol/conc. ammonia=9:1:0.1)=0.23; HPLC  $R_t$  =14.5 minutes; FAB-MS  $(M+H)^+$  =592.

The starting materials are prepared as follows:

15 a) 5(S)-Tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-tert-butyl-3-(3-methoxypropoxy)-phenyl]-octanoic acid [N-2-(morpholin-4-yl)-ethyl]-amide

A solution of 756 mg of 3(S)-isopropyl-5(S)-{1(S)-tert-butoxycarbonylamino-3(S)-isopropyl-4-[4-tert-butyl-3-(3-methoxypropoxy)-phenyl]-butyl}-tetrahydrofuran-2-one in 4 ml of  
20 4-(2-aminoethyl)-morpholine and 0.23 ml of glacial acetic acid is stirred for 4 hours at 65°C and is then concentrated by evaporation. The residue is partitioned between diethyl ether (30 ml) and a saturated sodium hydrogen carbonate solution (10  
25 ml), the aqueous phase is extracted with diethyl ether (2x30 ml), and the combined organic phases are dried over magnesium sulfate and concentrated. Purification of the residue by means of FC (70 g of silica gel, dichloromethane/methanol/conc.  
30 ammonia=98:2:1 after 96:4:1) yields the title compound in the form of a white foam:  $R_f$  (dichloromethane/methanol/conc. ammonia=9:1:0.1)=0.43; HPLC  $R_t$  =19.8 minutes.

b) 3(S)-Isopropyl-5(S)-{1(S)-tert-butoxycarbonylamino-3(S)-isopropyl-4-[4-tert-butyl-3-(3-methoxypropoxy)-phenyl]-butyl}-tetrahydrofuran-2-one

A solution of 1.24 g of 3(S)-isopropyl-5(S)-{4(R,S)-acetoxymethyl-1(S)-azido-3(S)-isopropyl-4(R,S)-[4-tert-butyl-3-(3-methoxypropoxy)-phenyl]-butyl}-tetrahydrofuran-2-one in 25 ml of ethanol is hydrogenated for a period of 28 hours in the presence of 2.4 g of 5% PdO/C (Engelhardt) at room temperature and under normal pressure. The reaction mixture is filtered over Celite 545 and washed with ethanol, and the residue obtained after concentration is dried under a high vacuum. The product so obtained (843 mg) is dissolved in 20 ml of dichloromethane, and 0.58 ml of N-diisopropylethylamine and a solution of 638 mg of di-tert-butyl dicarbonate in 5 ml of dichloromethane are added thereto in succession at 0°-5°C. The mixture is stirred at room temperature overnight, and then the solvent is removed in vacuo and the crude product is purified by means of FC (60 g of silica gel, hexane/ethyl acetate/conc. ammonia=80:20:1). The title compound is obtained in the form of a colourless oil:  $R_f$  (hexane/ethyl acetate/conc. ammonia=50:50:1)=0.90; HPLC  $R_t$  =26.2 minutes.

c) 3(S)-Isopropyl-5(S)-{4(R,S)-acetoxymethyl-1(S)-azido-3(S)-isopropyl-4(R,S)-[4-tert-butyl-3-(3-methoxypropoxy)-phenyl]-butyl}-tetrahydrofuran-2-one

A mixture of 1.15 g of 3(S)-isopropyl-5(S)-{4(R,S)-hydroxymethyl-1(S)-azido-3(S)-isopropyl-4(R,S)-[4-tert-butyl-3-(3-methoxypropoxy)-phenyl]-butyl}-tetrahydrofuran-2-one, 11 ml of acetic anhydride and 0.55 ml of pyridine is stirred overnight at room temperature. The reaction mixture is concentrated and the residue is partitioned between 100 ml of dichloromethane and 20 ml of water. The crude product obtained after working up by extraction is purified by FC (80 g of silica gel, hexane/ethyl

acetate=2:1). The title compound is obtained in the form of a yellowish oil:  $R_f$  (hexane/ethyl acetate=2:1)=0.66.

d) 3(S)-Isopropyl-5(S)-{4(R,S)-hydroxy-1(S)-azido-3(S)-isopropyl-4(R,S)-[4-tert-butyl-3-(3-methoxypropoxy)-phenyl]-butyl}-tetrahydrofuran-2-one

In a manner analogous to that described in Example 185c), 4-tert-butyl-3-(3-methoxy-propoxy)-bromobenzene (2.35 g), dissolved in 60 ml of tetrahydrofuran, is reacted with 4.86 ml of a 1 N n-butyllithium solution (in hexane) and then with a suspension of magnesium bromide in 20 ml of tetrahydrofuran (prepared from 380 mg of magnesium powder and 1.35 ml of 1,2-dibromoethane in). A solution of 1.46 g of 3(S)-isopropyl-5(S)-[1(S)-azido-3(S)-isopropyl-4-oxobutyl]-tetrahydrofuran-2-one in 6 ml of tetrahydrofuran is added dropwise to the resulting suspension at -70°C over a period of 20 minutes, and the mixture is then stirred for a further one hour. After working up by extraction, the crude product is purified by FC (300 g of silica gel, hexane/ethyl acetate=5:1 after 3:1). The title compound is obtained in the form of a pale yellow oil:  $R_f$  (hexane/ethyl acetate=2:1)=0.57; HPLC  $R_t$  =22.9 and 24.1 minutes (diastereoisomeric mixture).

e) 4-Tert-butyl-3-(3-methoxypropoxy)-bromobenzene

A suspension of 2.60 g of 5-bromo-2-tert-butyl-phenol, 4.34 g of 3-methoxypropyl bromide and 5.55 g of caesium carbonate in 40 ml of acetone is stirred at 60°C overnight. After cooling to room temperature, the mixture is filtered and the crude product obtained after concentration of the filtrate is purified by means of FC (80 g of silica gel, hexane/ethyl acetate=98:2). The title compound is obtained in the form of an oil:  $R_f$  (hexane/ethyl acetate=9:1)=0.56.

**EXAMPLE 85**

5 (S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(4-hydroxypiperidin-1-yl)ethyl]amide dihydrochloride

100 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(4-hydroxy-piperidin-1-yl)-ethyl]-amide are dissolved in 3 ml of 4N hydrochloric acid in dioxane at 0°C, and the mixture is stirred for 2 hours at 0°C. The reaction mixture is lyophilised and the title compound is obtained:  $R_f$  (dichloromethane/methanol=8:2)=0.08; HPLC  $R_t$  =8.85 minutes; FAB-MS (M+H)<sup>+</sup> =552.

15

The starting material is prepared as follows:

a) 5(S)-Tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(4-hydroxypiperidin-1-yl)-ethyl]-amide

20

102 mg of 2-{1(S)-tert-butoxycarbonylamino-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105e) and 0.5 g of N-(2-aminoethyl)-4-hydroxypiperidine are stirred for 2 hours at 80°C. The reaction mixture is purified by means of FC (60 g of silica gel, dichloromethane/methanol=4:1). The title compound is obtained:  $R_f$  (dichloromethane/methanol=4:1)=0.16.

25

**EXAMPLE 86**

30 (S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2,2-dimethyl-2-morpholino-ethyl)amide dihydrochloride

Analogously to Example 85, the title compound is obtained starting from 120 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2,2-dimethyl-2-morpholino-ethyl)-amide:  $R_f$  (dichloromethane/methanol=9:1)=0.07; HPLC  $R_t$  =9.22 minutes; FAB-MS  $(M+H)^+ =566$ .

The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 4-(2-amino-1,1-dimethyl-ethyl)-morpholine.

#### EXAMPLE 87

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(trans-2,6-dimethyl-morpholino)-ethyl]amide dihydrochloride

Analogously to Example 85, the title compound is obtained starting from 102 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(trans-2,6-dimethyl-morpholino)-ethyl]amide:  $R_f$  (dichloromethane/methanol=8:2)=0.27; HPLC  $R_t$  =9.56 minutes; FAB-MS  $(M+H)^+ =566$ .

The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 4-(2-aminoethyl)-trans-2,6-dimethyl-morpholine.

a) 4-(2-Amino-ethyl)-2,6-(trans)-dimethyl-morpholine

8.20 g of 4-(2-phthaloylaminoethyl)-trans-2,6-dimethyl-morpholine are stirred under reflux for 2 hours in 250 ml of ethyl alcohol with 2.76 ml of hydrazine hydrate. The reaction mixture is diluted with diethyl ether and then clarified by  
5 filtration. The filtrate is concentrated, yielding the crude title compound:  $R_f$  (dichloromethane/methanol/conc. ammonia=40:10:1)=0.21.

b) 4-(2-Phthaloylaminoethyl)-trans-2,6-dimethyl-morpholine  
10 10.16 g of N-(2-bromoethyl)-phthalimide and 11.50 g of trans-2,6-dimethylmorpholine are stirred for 30 minutes at 130°C. The reaction mixture is then partitioned between ice-water and ethyl acetate. The organic phases are concentrated by evaporation and the residue is purified by means of FC (240 g of  
15 silica gel, ethyl acetate/hexane=1:2). The title compound is obtained:  $R_f$  (ethyl acetate/hexane=1:2)=0.39.

#### EXAMPLE 88

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(cis-  
20 2,6-dimethyl-morpholino)ethyl]-amide dihydrochloride

Analogously to Example 85, the title compound is obtained starting from 97 mg of 5(S)-tert-butoxycarbonylamino-4(S)-  
25 hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(cis-2,6-dimethyl-morpholino)-ethyl]amide:  $R_f$  (dichloromethane/methanol=8:2)=0.21; HPLC  $R_t$  =9.38 minutes; FAB-MS  $(M+H)^+$  =566.

30 The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-

tetrahydrofuran-5-one (Example 105 e) and 4-(2-amino-ethyl)-cis-2,6-dimethyl-morpholine.

The 4-(2-amino-ethyl)-cis-2,6-dimethyl-morpholine is prepared analogously to Examples 87 a) and 87 b) from cis-2,6-dimethylmorpholine.

#### EXAMPLE 89

5 (S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-piperidinoethyl)amide dihydrochloride

Analogously to Example 85, the title compound is obtained staging from 74 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-piperidinoethyl)amide:  $R_f$  (dichloromethane/methanol=8:2)=0.09; HPLC  $R_t$  =9.55 minutes; FAB-MS  $(M+H)^+ = 536$ .

20 The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and N-(2-piperidinoethyl)amine.

25

#### EXAMPLE 90

5 (S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(4-methoxypiperidino)-ethyl]-amide dihydrochloride

30

Analogously to Example 85, the title compound is obtained starting from 74 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-

methoxypropyloxy)-phenyl]-octanoic acid N-[2-(4-methoxy-piperidino)ethyl]-amide:  $R_f$  (dichloromethane/methanol=8:2)=0.12; HPLC  $R_t$  =9.39 minutes; FAB-MS  $(M+H)^+$  =566.

5        The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 1-(2-aminoethyl)-4-methoxypiperidine.

10

      The 1-(2-amino-ethyl)-4-methoxypiperidine is prepared analogously to Examples 87 a) and 87 b) from 4-methoxypiperidine.

15    **EXAMPLE 91**

      5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-thiomorpholinoethyl)amide dihydrochloride

20        Analogously to Example 85, the title compound is obtained starting from 110 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-thiomorpholinoethyl)amide:  $R_f$  (dichloromethane/methanol=8:2)=0.17; HPLC  $R_t$   
25    =9.53 minutes; FAB-MS  $(M+H)^+$  =554.

      The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxy-carbonylamino-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-  
30    tetrahydrofuran-5-one (Example 105 e) and 4-(2-aminoethyl)thiomorpholine.

**EXAMPLE 92**



5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-hydroxypropyl)]amide hydrochloride

- 5 Analogously to Example 85, the title compound is obtained starting from 110 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-hydroxypropyl)]amide:  $R_f$  (dichloromethane/methanol=9:1)=0.07;  
10 HPLC  $R_t$  =9.65 minutes; FAB-MS  $(M+H)^+ =483$ .

- The starting material is prepared analogously to Example 85  
a) from 2-{1(S)-tert-butoxycarbonylamino-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4-(R)-methyl-  
15 tetrahydrofuran-5-one (Example 105 e) and 3-amino-1-propanol.

#### EXAMPLE 93

- 5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(4-hydroxybutyl)]amide hydrochloride  
20

- Analogously to Example 85, the title compound is obtained starting from 112 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(4-hydroxybutyl)]amide:  $R_f$  (dichloro-methane/methanol=9:1)=0.07;  
25 HPLC  $R_t$  =9.83 minutes; FAB-MS  $(M+H)^+ =497$ .

- The starting material is prepared analogously to Example 85  
30 a) from 2-{1(S)-tert-butoxycarbonylamino-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4-(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 4-amino-1-butanol.

**EXAMPLE 94**

5 (S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(4-acetoxybutyl)]amide hydrochloride

Analogously to Example 85, the title compound is obtained starting from 27 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(4-acetoxybutyl)]amide:  $R_f$  (dichloromethane/methanol=9:1)=0.16; HPLC  $R_t$  =11.53 minutes; FAB-MS  $(M+H)^+ =539$ .

The starting material is prepared as follows:

15

a) 5(S)-Tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(4-acetoxybutyl)]amide

30 ml of triethylamine, 2 mg of 4-(N,N'-dimethylamino)pyridine (DMAP) and 20 ml of acetic anhydride are added at 0°C to 116 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(4-hydroxybutyl)]amide (Example 93) in 5 ml of tetrahydrofuran. The reaction solution is stirred for 18 hours at room temperature. The reaction mixture is partitioned between diethyl ether and water/saturated sodium chloride solution. The organic phases are concentrated by evaporation and the residue is purified by FC (40 g of silica gel, eluant: dichloromethane/methanol=95:5). The title compound is obtained:  $R_f$  (dichloromethane/methanol=9:1)=0.60.

**EXAMPLE 95**

5 (S)-Amino-4 (S)-hydroxy-7 (S)-isopropyl-2 (R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-cyanopropyl)]amide hydrochloride

5 Analogously to Example 85, the title compound is obtained starting from 107 mg of 5 (S)-tert-butoxycarbonylamino-4 (S)-hydroxy-7 (S)-isopropyl-2 (R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-cyanopropyl)]amide:  $R_f$  (dichloromethane/methanol=9:1)=0.07; HPLC  
10  $R_t$  =10.76 minutes; FAB-MS  $(M+H)^+ =492$ .

The starting material is prepared analogously to Example 85  
a) from 2-{1 (S)-tert-butoxycarbonylamino-3 (S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4 (R)-methyl-  
15 tetrahydrofuran-5-one (Example 105 e) and 4-amino-butyronitrile.

#### EXAMPLE 96

5 (S)-Amino-4 (S)-hydroxy-7 (S)-isopropyl-2 (R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-methoxypropyl)]amide hydrochloride  
20

Analogously to Example 85, the title compound is obtained starting from 107 mg of 5 (S)-tert-butoxycarbonylamino-4 (S)-hydroxy-7 (S)-isopropyl-2 (R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-methoxypropyl)]amide:  $R_f$  (dichloromethane/methanol=8:2)=0.34; HPLC  $R_t$  =10.70 minutes; FAB-MS  $(M+H)^+ =497$ .  
25

The starting material is prepared analogously to Example 85  
30 a) from 2-{1 (S)-tert-butoxycarbonylamino-3 (S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4 (R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 3-methoxy-propylamine.

**EXAMPLE 97**

5 (S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-acetylamin

10 Analogously to Example 85, the title compound is obtained starting from 82 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-acetylamin

ethyl)]amide:  $R_f$  (dichloromethane/methanol=8:2)=0.17; HPLC  $R_t$  =9.54 minutes; FAB-MS  $(M+H)^+$  =510.

15 The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxy-carbonylamino-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxy propyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and N-acetyl-ethylenediamine.

20 **EXAMPLE 98**

5 (S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(2-pyridyl)-ethyl]}-amide hydrochloride

25 Analogously to Example 85, the title compound is obtained starting from 118 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(2-pyridyl)-ethyl]}-amide:  $R_f$  (dichloromethane/methanol=9:1)=0.09; HPLC  $R_t$

30 =8.88 minutes; FAB-MS  $(M+H)^+$  =530.

The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino-3(S)-isopropyl-4-[4-

methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 2-(2-aminoethyl)-pyridine.

5 **EXAMPLE 99**

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N'-oxomorpholino)ethyl]-amide hydrochloride

10 Analogously to Example 85, the title compound is obtained starting from 82 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N'-oxomorpholino)ethyl]amide:  $R_f$

15 (dichloromethane/methanol=8:2)=0.07; HPLC  $R_t$  =9.04 minutes; FAB-MS  $(M+H)^+$  =554.

The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 4-(2-aminoethyl)-N-oxo-morpholine.

The starting material is prepared as follows:

25 a) 4-(2-Aminoethyl)-N-oxo-morpholine

2.8 g of 4-(2-benzyloxycarbonylaminoethyl)-N-oxo-morpholine are hydrogenated in the presence of 0.30 g of 10% Pd/C in methanol for 10 minutes at room temperature and under normal pressure. The reaction mixture is filtered and concentrated by evaporation. The crude title compound is obtained:  $^1H$ -NMR ( $CD_3$  OD),  $\delta$ (ppm)=4.90 (2H, s), 4.20 (1H, m), 3.87-2.80 (10H, m), 2.50 (1H, m)

b) 4-(2-Benzyloxycarbonylaminoethyl)-N-oxo-morpholine

6 portions, each of 1.48 ml, of 30% hydrogen peroxide are added at 60°C, with stirring, at intervals of 12 hours, to 10.6 g of 4-(2-benzyloxycarbonylaminoethyl)-morpholine in 12 ml of methanol. Saturated sodium sulfite solution is added carefully to the cooled reaction mixture until the excess peroxide has been destroyed. The methanol is evaporated off, and the resulting suspension is taken up in ethyl acetate/methanol 99:1. The mixture is dried with magnesium sulfate and is filtered, and the filtrate is concentrated by evaporation. Crystallisation from ethyl acetate yields the title compound:  $R_f$  (dichloromethane/methanol=8:2)=0.17; m.p. 163°C.

**EXAMPLE 100**

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[3-(tert-butylsulfonyl)-propyl]}-amide hydrochloride

Analogously to Example 85, the title compound is obtained starting from 110 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[3-(tert-butylsulfonyl)-propyl]}-amide:  $R_f$  (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.45; HPLC  $R_t$  =11.27 minutes; FAB-MS  $(M+H)^+$  =587.

The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 3-amino-1-(tert-butylsulfonyl)propane.

The starting material is prepared as follows:

a) 3-Amino-1-(tert-butylsulfonyl)-propane

1.0 g of 3-aminopropyl-(tert-butylsulfonyl)-propane is dissolved at 0°C in 30 ml of water. 2.14 g of potassium permanganate and 2 ml of 4 N hydrochloric acid in 30 ml of water are added in succession, and the mixture is stirred overnight at 0°C. The dark suspension is filtered off and washed with 100 ml of hot water. 50 ml of toluene are added to the filtrate, and the mixture is concentrated. The precipitated white crystals are purified by means of FC (10 g of silica gel, ethyl acetate/methanol/conc. ammonia=80:15:5). The title compound is obtained:  $R_f$  (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.20.

**EXAMPLE 101**

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[3-(ethylsulfonyl)-propyl]}-amide hydrochloride

Analogously to Example 85, the title compound is obtained starting from 44 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[3-(ethylsulfonyl)-propyl]}-amide:  $R_f$  (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.26; HPLC  $R_t$  =10.40 minutes; FAB-MS (M+H)<sup>+</sup> =559.

25

The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 3-amino-1-(ethylsulfonyl)propane.

30

The starting material is prepared as follows:

a) 3-Amino-1-(ethylsulfonyl)-propane

1.0 g of 3-aminopropyl-ethyl sulfide is placed in 35 ml of methanol at 0°C; 15.5 g of oxone in 35 ml of water are added and the mixture is stirred at 0°C for 4 hours. 200 ml of water are added and the mixture is extracted with 3 x 150 ml of dichloromethane. The organic extracts are concentrated by evaporation and purified by FC (10 g of silica gel, ethyl acetate/methanol/conc. ammonia=80: 15:5). The title compound is obtained:  $R_f$  (ethyl acetate/methanol/conc. ammonia=80: 15:5)=0.15.

#### EXAMPLE 102

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(ethylsulfonyl)-ethyl]}-amide hydrochloride

Analogously to Example 85, the title compound is obtained starting from 90 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(ethylsulfonyl)-ethyl]}-amide:  $R_f$  (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.39; HPLC  $R_t$  =10.50 minutes; FAB-MS (M+H)<sup>+</sup> =545.

The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 2-amino-1-(ethylsulfonyl)ethane.

#### EXAMPLE 103

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(N-butylsulfonyl)-ethyl]}-amide hydrochloride



Analogously to Example 85, the title compound is obtained starting from 67 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(N-butylsulfonyl)-ethyl]}-amide:  $R_f$  (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.41; HPLC  $R_t$  =12.52 minutes; FAB-MS  $(M+H)^+$  =588.

The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 2-aminoethyl-(N-butyl)sulfonamide.

#### EXAMPLE 104

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(N,N-dimethylsulfonyl)-ethyl]}-amide hydrochloride

Analogously to Example 85, the title compound is obtained starting from 120 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(N,N-dimethylsulfonyl)-ethyl]}-amide:  $R_f$  (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.43; HPLC  $R_t$  =11.03 minutes; FAB-MS  $(M+H)^+$  =560.

The starting material is prepared analogously to Example 85 a) from 2-{1(S)-tert-butoxycarbonylamino-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one (Example 105 e) and 2-aminoethyl-(N,N-dimethyl)sulfonamide.

**EXAMPLE 105**

5 (S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-carbamoyl-propyl)]-amide hydrochloride

84 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-carbamoyl-propyl)]-amide are dissolved in 3 ml of 4 N hydrochloric acid in dioxane at 0°C and the mixture is stirred for 2 hours at 0°C. The reaction mixture is lyophilised. The title compound is obtained:  $R_f$  (dichloromethane/methanol=9:1)=0.04; HPLC  $R_t$  =9.44 minutes; HR FAB-MS  $(M+H)^+ = 510$ .

15

The starting materials are prepared as follows:

a) 5(S)-Tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-carbamoyl-propyl)]-amide

50 mg of tetrabutylammonium fluoride trihydrate are added to 115 mg of 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyltrimethylsilyloxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid [N-(3-carbamoyl-propyl)]-amide in 4 ml of dimethylformamide at 0°C. The reaction mixture is stirred for a further 5 hours at room temperature and then concentrated by evaporation. 20 ml of saturated sodium hydrogen carbonate solution are added to the evaporation residue and the mixture is extracted repeatedly with ethyl acetate. The organic phases are washed with saturated sodium chloride solution and concentrated by evaporation. The residue is purified by means of FC (18 g of silica gel,

dichloromethane/methanol=9:1). The title compound is obtained:  
R<sub>f</sub> (dichloromethane/methanol=9:1): 0.24.

b) 5(S)-Tert-butoxycarbonylamino-4(S)-tert-butyl-  
5 butyldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-carbamoyl-propyl)]-amide

67 µl of triethylamine, 34 mg of 4-aminobutyric acid amide  
hydrochloride and 38 µl of cyanophosphonic acid diethyl ester  
10 are added in succession to 128 mg of 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyl-  
butyldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-  
phenyl]-octanoic acid in 8 ml of dimethylformamide at 0°C. The  
reaction mixture is stirred for a further 18 hours at room  
15 temperature. The reaction mixture is concentrated by evaporation  
and 20 ml of 10% citric acid solution and ice are added to the  
residue. The mixture is extracted repeatedly with ethyl acetate  
and the organic phases are then washed with saturated sodium  
hydrogen carbonate solution and saturated sodium chloride  
20 solution. After concentration by evaporation, the residue is  
purified by means of FC (70 g of silica gel,  
dichloromethane/methanol=9:1). The title compound is obtained:  
R<sub>f</sub> (dichloromethane/methanol=9:1)=0.38.

25 c) 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyl-  
butyldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid

4.45 g of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-  
isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-  
30 phenyl]-octanoic acid (crude) are stirred in 45 ml of  
dimethylformamide with 2.36 g of tert-butyl-  
dimethylsilyl chloride and 2.03 g of imidazole for 6 days at room temperature.  
The mixture is concentrated by evaporation and the residue is

partitioned between 10% citric acid solution and ethyl acetate. The organic phase is concentrated and stirred in 20 ml of tetrahydrofuran, 8 ml of water and 20 ml of acetic acid at room temperature for 16 hours. After concentration by evaporation,  
5 ice/water is added to the residue and the mixture is then extracted with ethyl acetate. The title compound is obtained from the organic phase after FC (260 g of silica gel, ethyl acetate/hexane=1:1):  $R_f$  (ethyl acetate/hexane=1:1)=0.32.

- 10 d) 5(S)-Tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid

28.5 ml of 1 N lithium hydroxide solution are added to 3.6 g of 2-{1(S)-tert-butoxycarbonylamino-3(S)-isopropyl-4-[4-  
15 methoxy-3-(3-methoxy-propyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one in 210 ml of 1,2-dimethoxyethane/water (2:1) at room temperature. The reaction mixture is stirred at room temperature for a further 1 hour and then concentrated by evaporation. Ice and 10% aqueous citric acid solution are added  
20 to the residue. Repeated extraction with chloroform yields the crude title compound:  $R_f$  (ethyl acetate/hexane=1:1)=0.05; HPLC  $R_t$  =16.41 minutes.

- 25 e) 2-{1(S)-tert-butoxycarbonylamino-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-butyl}-4(R)-methyl-tetrahydrofuran-5-one

2.02 g of p-toluenesulfonic acid (monohydrate) are added to 5.6 g of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-  
30 phenyl]-octanoic acid (N-butyl)-amide (Example 32) in 240 ml of chloroform at room temperature and the mixture is stirred at room temperature for a further 18 hours. The reaction mixture is concentrated by evaporation and the residue is partitioned

between diethyl ether and 0.1N hydrochloric acid. The organic phases are concentrated by evaporation and the title compound is obtained from the residue after FC (160 g of silica gel, eluant: ethyl acetate/hexane 1:1):  $R_f$  (ethyl acetate/hexane=2:1)=0.47;

5 m.p. 86°-87°C.

#### EXAMPLE 106

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[3-(1H-tetrazol-5-yl)-propyl]}-amide hydrochloride

Analogously to Example 105, the title compound is obtained starting from 47 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[3-(1H-tetrazol-5-yl)-propyl]}-amide and after lyophilisation:  $R_f$  (dichloromethane/methanol=8:2)=0.46; HPLC  $R_t$  =9.97 minutes; FAB-MS (M+H)<sup>+</sup> =535.

20 The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyltrimethylsilyloxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 3-(1H-tetrazol-5-yl)-propylamine.

25

#### EXAMPLE 107

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[3-(1H-imidazol-5-yl)-propyl]}-amide hydrochloride

30

Analogously to Example 105, the title compound is obtained starting from 43 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-

methoxypropyloxy)-phenyl]-octanoic acid {N-[3-(1H-imidazol-5-yl)-propyl]}-amide and after lyophilisation:  $R_f$  (dichloromethane/methanol=8:2)=0.13; HPLC  $R_t$  =8.83 minutes; FAB-MS  $(M+H)^+ =533$ .

5

The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyltrimethylsilyloxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 3-(1H-imidazol-5-yl)-propylamine.

**EXAMPLE 108**

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-3-(3-methyl-1,2,4-oxadiazol-5-yl)-propyl}-amide hydrochloride

Analogously to Example 105, the title compound is obtained starting from 140 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[3-(3-methyl-1,2,4-oxadiazol-5-yl)-propyl]}-amide and after lyophilisation:  $R_f$  (dichloromethane/methanol=9:1)=0.12; HPLC  $R_t$  =11.05 minutes; FAB-MS  $(M+H)^+ =549$ .

The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyltrimethylsilyloxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 3-(3-methyl-1,2,4-oxadiazol-5-yl)-propylamine.

30

a) 3-(3-Methyl-1,2,4-oxadiazol-5-yl)-propylamine

272 mg of 3-methyl-5-[3-(N-phthaloylamino)propyl]-1,2,4-oxadiazole in 10 ml of ethyl alcohol are stirred for 2 hours

under reflux with 146 ml of hydrazine hydrate. The reaction mixture is diluted with diethyl ether and then clarified by filtration. The filtrate is concentrated by evaporation and yields the crude title compound:  $R_f$  (dichloromethane/methyl alcohol/conc. ammonia=40:10:1)=0.37.

b) 3-Methyl-5-[3-(N-phthaloylamino)propyl]-1,2,4-oxadiazole

0.84 g of sodium hydride dispersion (80% ) is added to 2.08 g of acetamidoxime in 200 ml of tetrahydrofuran at room temperature and the mixture is stirred at 60°C for 2 hours. A solution of 2.47 g of 4-(N-phthaloylamino)butyric acid methyl ester in 30 ml of tetrahydrofuran is then added and stirring is continued at 60°C for a further 3 hours. The reaction mixture is poured onto 1N hydrochloric acid/ice and extracted repeatedly with ethyl acetate. The dried organic phases are concentrated by evaporation and the residue is boiled in 60 ml of xylene for 3 hours on a water-separator. The solvent is evaporated off and the title compound is obtained from the residue after FC (40 g of silica gel, ethyl acetate/hexane=1:1):  $R_f$  (ethyl acetate/hexane=1:1)=0.26.

#### EXAMPLE 109

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-aminopropyl)]-amide dihydrochloride

Analogously to Example 105, the title compound is obtained starting from 125 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-tert-butoxycarbonylamino-propyl)]-amide and after lyophilisation:  $R_f$  (dichloromethane/methanol/conc. ammonia=40:10:1)=0.08; HPLC  $R_t$  =6.48 minutes; FAB-MS  $(M+H)^+$  =482.

The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyltrimethylsilyloxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 3-tert-butoxycarbonylamino-propylamine.

**EXAMPLE 110**

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-dimethylamino-ethyl)]-amide dihydrochloride

Analogously to Example 105, the title compound is obtained starting from 38 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-dimethylamino-ethyl)]-amide and after lyophilisation:  $R_f$  (dichloromethane/methanol/conc. ammonia=350:50:1)=0.03; HPLC  $R_t$  =8.61 minutes; FAB-MS  $(M+H)^+ = 496$ .

The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyltrimethylsilyloxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 2-dimethylaminoethylamine.

**EXAMPLE 111**

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-morpholinoethyl)amide dihydrochloride

Analogously to Example 105, the title compound is obtained starting from 70 mg of 5(S)-tert-butoxycarbonylamino-4(S)-



hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-morpholinoethyl)amide and after lyophilisation:  $R_f$  (dichloromethane/methanol/conc. ammonia=350:50:1)=0.15; HPLC  $R_t$  =8.74 minutes; FAB-MS  $(M+H)^+ = 538$ .

The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyltrimethylsilyloxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 4-(2-aminoethyl)-morpholine.

#### EXAMPLE 112

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(3-morpholinopropyl)amide dihydrochloride

Analogously to Example 105, the title compound is obtained starting from 37 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(3-morpholinopropyl)amide and after lyophilisation:  $R_f$  (dichloromethane/methanol/conc. ammonia=350:50:1)=0.11; HPLC  $R_t$  =8.68 minutes; FAB-MS  $(M+H)^+ = 552$ .

The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyltrimethylsilyloxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 4-(3-aminopropyl)-morpholine.

#### EXAMPLE 113

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(1,1-dioxothiomorpholino)ethyl]amide dihydrochloride

5 Analogously to Example 105, the title compound is obtained starting from 100 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(1,1-dioxothiomorpholino)ethyl]-amide and after lyophilisation:  $R_f$   
10 (dichloromethane/methanol=8:2)=0.30; HPLC  $R_t$  =9.29 minutes; FAB-MS  $(M+H)^+ =586$ .

The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyl-  
15 dimethylsilyloxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 2-(1,1-dioxothiomorpholino)-ethylamine.

#### EXAMPLE 114

20 5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-ethoxycarbonyl-ethyl)amide hydrochloride

Analogously to Example 105, the title compound is obtained  
25 starting from 32 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-ethoxycarbonyl-ethyl)]-amide and after lyophilisation:  $R_f$   
(dichloromethane/methanol=9:1)=0.17; HPLC  $R_t$  =11.31 minutes;  
30 FAB-MS  $(M+H)^+ =525$ .

The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-

butyldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and  $\beta$ -alanine ethyl ester hydrochloride.

#### 5 **EXAMPLE 115**

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carboxy-ethyl)]-amide hydrochloride

- 10 Analogously to Example 105, the title compound is obtained starting from 60 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carboxy-ethyl)]-amide and after lyophilisation:  $R_f$
- 15 (dichloromethane/methanol=8:2)=0.28; HPLC  $R_t$  =9.74 minutes; FAB-MS  $(M+H)^+ =497$ .

The starting material is prepared as follows:

- 20 a) 5(S)-Tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carboxyethyl)]-amide
- 70 mg of 5(S)-tert-butoxyamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic
- 25 acid [N-(2-ethyloxy-carbonyl-ethyl)]-amide (Example 114) are stirred in 2 ml of methanol with 224  $\mu$ l of 1 N sodium hydroxide at room temperature for 18 hours. After evaporation of the methanol, 250  $\mu$ l of 1 N hydrochloric acid are added and the product is extracted with ethyl acetate. The organic phase is
- 30 concentrated by evaporation and the residue is purified by means of FC (10 g of silica gel, eluant: dichloromethane/methanol=8:2). The title compound is obtained:  $R_f$  (dichloromethane/methanol=9:1)=0.12.

**EXAMPLE 116**

5 (S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-methoxycarbonyl-ethyl)]-amide hydrochloride

Analogously to Example 105, the title compound is obtained starting from 90 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-methoxycarbonyl-ethyl)]-amide and after lyophilisation:  $R_f$  (dichloromethane/methanol=9:1)=0.13; HPLC  $R_t$  =10.80 minutes; FAB-MS (M+H)<sup>+</sup> =525.

15 The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butylldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 4-aminobutyric acid methyl ester hydrochloride.

**EXAMPLE 117**

(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-carboxypropyl)]-amide hydrochloride

25 Analogously to Example 105, the title compound is obtained starting from 38 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(3-carboxypropyl)]-amide and after lyophilisation:  $R_f$  (dichloromethane/methanol=8:2)=0.55; HPLC  $R_t$  =9.85 minutes; FAB-MS (M+H)<sup>+</sup> =511.

The starting material is prepared as follows:

5(S)-Tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-  
2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic  
5 acid [N-(3-carboxypropyl)]-amide

Analogously to Example 115 a), the title compound is  
prepared from 5(S)-tert-butoxycarbonyl-amino-4(S)-hydroxy-7(S)-  
isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxy-propyloxy)-  
phenyl]-octanoic acid [N-(3-methyloxycarbonylpropyl)]-amide  
10 (Example 116).

#### EXAMPLE 118

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-  
methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-  
15 carbamoylethyl)]-amide hydrochloride

Analogously to Example 105, the title compound is obtained  
starting from 93 mg of 5(S)-tert-butoxycarbonylamino-4(S)-  
hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-  
20 methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carbamoylethyl)]-  
amide and after lyophilisation:  $R_f$   
(dichloromethane/methanol=8:2)=0.15; HPLC  $R_t$  =9.33 minutes; FAB-  
MS  $(M+H)^+ = 496$ .

25 The starting material is prepared analogously to Example  
105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-  
butyldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-  
(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and  
3-aminopropionic acid amide hydrochloride.

#### EXAMPLE 119

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(4-carbamoylbutyl)-amide hydrochloride

- 5 Analogously to Example 105, the title compound is obtained starting from 85 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(4-carbamoylbutyl)]-amide and after lyophilisation:  $R_f$
- 10 (dichloromethane/methanol=8:2)=0.20; HPLC  $R_t$  =9.72 minutes; FAB-MS  $(M+H)^+ =524$ .

The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyltrimethylsilyloxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 5-aminopentanoic acid amide hydrochloride.

#### EXAMPLE 120

- 20 5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[3-(N-methylcarbamoyl)propyl]amide hydrochloride

- Analogously to Example 105, the title compound is obtained starting from 89 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[3-(N-methylcarbamoyl)propyl]amide and after lyophilisation:  $R_f$
- 25 (dichloromethane/methanol=9:1)=0.04; HPLC  $R_t$  =9.74 minutes; FAB-MS  $(M+H)^+ =524$ .

The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-

butyldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 4-amino-N-methyl-butyric acid amide hydrochloride.

5 **EXAMPLE 121**

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-{3-[N-(2-methoxyethyl) carbamoyl]propyl}-amide hydrochloride

- 10 Analogously to Example 105, the title compound is obtained starting from 92 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-{3-[N-(2-methoxyethyl) carbamoyl]propyl}-amide and after lyophilisation:
- 15  $R_f$  (dichloromethane/methanol=8:2)=0.28; HPLC  $R_t$  =10.14 minutes; FAB-MS  $(M+H)^+ = 568$ .

- The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyl-20 butyldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 4-aminobutyric acid N-(2-methoxyethyl)amide hydrochloride.

The starting material is prepared as follows:

25

4-Aminobutyric acid N-(2-methoxyethyl)amide hydrochloride

- 2.95 g of 4-benzyloxycarbonylamino-2-methoxyethylamide are hydrogenated in the presence of 0.24 g of 10% Pd/C in 150 ml of methanol and 100 ml of 0.1 N hydrochloric acid for 2 hours at room temperature and under normal pressure. The reaction mixture is filtered and concentrated by evaporation. The crude title compound is obtained:  $^1H$  NMR ( $CD_3$
- 30

OD),  $\delta$  (ppm)=4.92 (4H, s), 3.53-3.20 (4H, m), 3.34 (3H, 2.96 (2H, t, J=12 Hz), 2.37 (2H, t, J=12 Hz), 1.93 (2H, m).

b) 4-Benzyloxycarbonylaminobutyric acid N-(2-methoxyethyl)amide 5.02 g of 4-benzyloxycarbonylaminobutyric acid methyl ester are stirred under reflux in 35 ml of ethanol with 15 ml of 2-methoxyethylamine for 5 days. The reaction mixture is concentrated by evaporation and the residue is purified by means of FC (240 g of silica gel, dichloromethane/methanol=95:5). The title compound is obtained:  $R_f$  (dichloromethane/methanol=95:5)=0.33.

#### EXAMPLE 122

5(S)-Amino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(4-morpholino-4-oxo-butyl)amide hydrochloride

Analogously to Example 105, the title compound is obtained starting from 110 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(4-morpholino-4-oxo-butyl)amide and after lyophilisation:  $R_f$  (dichloromethane/methanol=9:1)=0.06; HPLC  $R_t$  =10.17 minutes; FAB-MS  $(M+H)^+$  =580.

25

The starting material is prepared analogously to Example 105 a) and 105 b) from 5(S)-tert-butoxycarbonylamino-4(S)-tert-butyldimethylsilyloxy-7(S)-isopropyl-2(R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 4-aminobutyric acid N'-(4-morpholino)amide hydrochloride.

30

#### EXAMPLE 123



5 (S)-Amino-4 (S)-hydroxy-7 (S)-isopropyl-2 (R)-methyl-8-4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-2,2-dimethyl-ethyl)]-amide hydrochloride

- 5 Analogously to Example 105, the title compound is obtained starting from 66 mg of 5 (S)-tert-butoxycarbonylamino-4 (S)-hydroxy-7 (S)-isopropyl-2 (R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-2,2-dimethyl-ethyl)]-amide and after lyophilisation:  $R_f$
- 10 (dichloromethane/methanol=8:2)=0.27; HPLC  $R_t$  =12.10 minutes; FAB-MS  $(M+H)^+ =524$ .

The starting material is prepared analogously to Example 105 a) and 105 b) from 5 (S)-tert-butoxycarbonylamino-4 (S)-tert-butyl-15 dimethylsilyloxy-7 (S)-isopropyl-2 (R)-methyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid (Example 105 c) and 3-amino-2,2-dimethyl-propionic acid amide hydrochloride.

#### EXAMPLE 124

- 20 5 (S)-Amino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-morpholinoethyl)amide dihydrochloride

- 25 3.09 g of 5 (S)-tert-butoxycarbonylamino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-morpholinoethyl)amide are dissolved in 40 ml of 4 N hydrochloric acid in dioxane at 0°C and the solution is stirred at 0°C for 2 hours. The reaction mixture is lyophilised and the title compound is obtained:  $R_f$
- 30 (dichloromethane/methanol=8:2)=0.27; HPLC  $R_t$  =9.52 minutes; HR FAB-MS  $(M+H)^+ =566$ .

The starting materials are prepared as follows:

a) 5(S)-Tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-morpholino-ethyl)amide

1.30 g of p-toluenesulfonic acid (monohydrate) are added to  
5 4.18 g of 3-tert-butoxycarbonyl-5(S)-{2(S)-[N-(2-morpholino-ethyl)carbamoyl]-2(S)-isopropyl-ethyl}-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine in 160 ml of methanol at 0°C. The reaction solution is stirred at room temperature for a further 18 hours.  
10 After evaporation of the solvent, 200 ml of 0.1 N sodium hydroxide are added to the residue and extraction is carried out with dichloromethane. The organic extracts are concentrated by evaporation and purified by FC (230 g of silica gel, dichloromethane/methanol=95:5). The title compound is obtained:  
15  $R_f$  (dichloromethane/methanol=9:1)=0.55.

b) 3-Tert-butoxycarbonyl-5(S)-{2(S)-[N-(2-morpholino-ethyl)-carbamoyl]-2(S)-isopropyl-ethyl}-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-  
20 1,3-oxazolidine

1.09 ml of triethylamine, 1.02 ml of 4-(2-aminoethyl)-morpholine and 1.19 ml of cyanophosphonic acid diethyl ester are added in succession to 3.88 g of 3-tert-butoxycarbonyl-5(S)-[2(S)-carboxy-3-methyl-butyl]-4(S)-{2(S)-isopropyl-3-[4-methoxy-  
25 3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-2,3-oxazolidine in 190 ml of dimethylformamide at 0°C. The reaction mixture is stirred at room temperature for a further 18 hours. The reaction mixture is concentrated by evaporation and the residue is partitioned between diethyl ether and saturated  
30 sodium hydrogen carbonate solution. The organic phases are washed with saturated sodium chloride solution and concentrated by evaporation. The residue is purified by FC (230 g of silica

gel, dichloromethane/methanol=95:5). The title compound is obtained:  $R_f$  (dichloromethane/methanol=95:5)=0.25.

c) 3-Tert-butoxycarbonyl-5(S) - (2(S) -carboxy-3-methyl-butyl) -4(S) -{2(S) -isopropyl-3- [4-methoxy-3- (3-methoxypropyloxy) -phenyl] -propyl} -2,2-dimethyl-1,3-oxazolidine

53 g of 3-tert-butoxycarbonyl-5(S) - (2(S) -formyl-3-methyl-butyl) -4(S) -{2(S) -isopropyl-3- [4-methoxy-3- (3-methoxypropyloxy) -phenyl] -propyl} -2,2-dimethyl-1,3-oxazolidine are dissolved in 470 ml of toluene, and, at 0°C, 470 ml of water, 79.1 g of potassium permanganate and 9.7 g of tetrabutylammonium bromide are added in succession thereto. The reaction mixture is stirred for a further 48 hours at 0°-5°C, and then, at 10°C, 1.2 liters of 10% sodium sulfite solution are added. After a further 30 minutes, 1.95 liters of 10% citric acid solution and 1.2 liters of water are added. The product is extracted by repeated extraction with ethyl acetate. The extracts are concentrated by evaporation and purified by FC (2.3 kg of silica gel, ethyl acetate/hexane=3:7). The title compound is obtained:  $R_f$  (ethyl acetate/hexane=1:2)=0.21.

d) 3-Tert-butoxycarbonyl-5(S) - (2(S) -formyl-3-methyl-butyl) -4(S) -{2(S) -isopropyl-3- [4-methoxy-3- (3-methoxypropyloxy) -phenyl] -propyl} -2,2-dimethyl-1,3-oxazolidine

100 g of molecular sieve (0.3 nm) and 16.6 g of N-methylmorpholine-N-oxide are added to 53 g of 3-tert-butoxycarbonyl-5(S) - (3-hydroxy-2(S) -isopropyl-propyl) -4(S) -{2(S) -isopropyl-3- [4-methoxy-3- (3-methoxypropyloxy) -phenyl] -propyl} -2,2-dimethyl-1,3-oxazolidine in 1.8 liters of dichloromethane at room temperature. The reaction mixture is stirred for 10 minutes and then 1.60 g of tetrapropylammonium perruthenate are added. The reaction mixture is stirred for a further 30 minutes and then filtered. The filtrate is diluted

with dichloromethane and then washed in succession with 2M sodium sulfite solution, saturated sodium chloride solution and 1 M copper(II) sulfate. The organic phase is concentrated by evaporation and the crude title compound is obtained:  $R_f$  (ethyl acetate/hexane=1:2)=0.43.

e) 3-Tert-butoxycarbonyl-5(S)-(3-hydroxy-2(S)-isopropyl-propyl)-4(S)-2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine

3.7 g of 3-tert-butoxycarbonyl-5(S)-(3-benzyloxy-2(S)-isopropyl-propyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine are hydrogenated in the presence of 1.0 g of 5% Pd/C in 50 ml of tetrahydrofuran for 15 minutes at room temperature and under normal pressure. The reaction mixture is filtered and concentrated by evaporation. The residue is purified by means of FC (140 g of silica gel, ethyl acetate/hexane=1:2). The title compound is obtained:  $R_f$  (ethyl acetate/hexane=1:2)=0.28.

f) 3-Tert-butoxycarbonyl-5(S)-(3-benzyloxy-2(S)-isopropyl-propyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (A)

and

3-tert-butoxycarbonyl-5(R)-(3-benzyloxy-2(S)-isopropyl-propyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (B)

10.9 ml of 2,2-dimethoxypropane and 10 mg of p-toluenesulfonic acid (monohydrate) are added to 7.0 g of 5(S)-tert-butoxycarbonylamino-4(R,S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octyl-benzyl ether in 1.86 liters of dichloromethane at room temperature. The reaction mixture is stirred at room temperature for a further 24 hours.

After concentration by evaporation, the residue is purified by FC (1 kg of silica gel and dichloromethane/diethyl ether=96:4). The title compounds are obtained:

5           A)  $R_f$  (dichloromethane/tert-butyl methyl ether)=0.36

          B)  $R_f$  (dichloromethane/tert-butyl methyl ether)=0.44

          g) 5(S)-Tert-butoxycarbonylamino-4(R,S)-hydroxy-2(S),7(S)-  
10 diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octyl-  
benzyl ether

          51.1 g of magnesium chips are placed in 1.4 liters of  
tetrahydrofuran at 55°C. A solution of 380 g of 2(S)-  
bromomethyl-3-methyl-butyl-benzyl ether, 30.2 ml of 1,2-  
15 dibromoethane in 0.8 liter of tetrahydrofuran at 55°C is added  
dropwise over a period of 30 minutes. The reaction mixture is  
stirred for a further 20 minutes at 55°C and then cooled to 5°C.  
A solution of 190 g of 2(S)-tert-butoxycarbonylamino-4(S)-  
isopropyl-5-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-pentanal  
20 in 0.7 liter of tetrahydrofuran is then added dropwise. The  
reaction mixture is stirred for a further 3 hours at room  
temperature, and then, at 5°C, saturated ammonium chloride  
solution is added and extraction is carried out with diethyl  
ether. The extracts are concentrated by evaporation and purified  
25 by FC (4 kg of silica gel, ethyl acetate/hexane=1:3). The title  
compound is obtained in the form of a diastereoisomeric mixture:  
 $R_f$  (ethyl acetate/hexane=1:2)=0.26; HPLC  $R_t$  =22.67 and 22.81  
(40:60).

30           h) 2(S)-Tert-butoxycarbonylamino-4(S)-isopropyl-5-[4-  
methoxy-3-(3-methoxy-propyloxy)-phenyl]-pentanal

          The title compound is prepared analogously to Example 1 c)  
to 1 g), except that in step 1 g) instead of 2(S)-isopropyl-3-

(p-tert-butyl-phenyl)-propanol there is used 2(R)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propanol. That compound is prepared as follows:

- 5           i) 2(R)-Isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propanol

186 g of 2(R)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propionic acid in 0.5 liter of tetrahydrofuran are added dropwise at room temperature to a stirred mixture of 27.2 g of sodium borohydride in 1.5 liters of tetrahydrofuran. After 45 minutes a solution of 76.2 g of iodine in 1 liter of tetrahydrofuran is added dropwise. The reaction mixture is stirred for 4 days and then 1 liter of methanol is carefully added dropwise. After evaporation of the solvent the residue is taken up in 2 liters of 2 N hydrochloric acid and extracted repeatedly with ethyl acetate. The organic extracts are washed in succession with water, saturated sodium thiosulfate solution, water/saturated sodium chloride solution (1:1), 0.1 N sodium hydroxide solution and saturated sodium chloride solution. The organic extracts are concentrated by evaporation and purified by FC (2.4 kg of silica gel, ethyl acetate/hexane=1:4). The title compound is obtained:  $R_f$  (ethyl acetate/hexane=1:1)=0.28.

- 25           k) 2(R)-Isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propionic acid

0.434 liter of 30% hydrogen peroxide is slowly added to 300 g of 4(R)-benzyl-3-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propionyl}-oxazolidin-2-one in 4.8 liters of tetrahydrofuran/water (3:1) at 0°C. After the addition of 31.2 g of lithium hydroxide, the mixture is stirred for 3 hours at 0°-20°C. 2.55 liters of 1.5 M sodium sulfite solution are then added to the reaction mixture at 0°-15°C and stirring

is continued for a further 30 minutes. 1 liter of saturated sodium hydrogen carbonate solution is added and the tetrahydrofuran is evaporated off. The aqueous solution is washed repeatedly with dichloromethane and then acidified with 2N hydrochloric acid (pH 3.0). Extraction with dichloromethane and subsequent evaporation of the solvent yield the title compound:  $R_f$  (ethyl acetate/hexane=2:1)=0.30; m.p. 43.5°-44°C.

1) 4(R)-Benzyl-3-{2(R)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propionyl}-oxazolidin-2-one

600 ml of tetrahydrofuran are added to a solution of 600 ml of 1 M lithium hexamethyl-disilazide and the mixture is stirred at -70°C. Then a solution of 156.6 g of 4(R)-benzyl-3-isovaleroyl-oxazolidin-2-one in 500 ml of tetrahydrofuran is added dropwise and the reaction mixture is stirred for a further 75 minutes at -70°C. Then a solution of 145 g of 4-methoxy-3-(3-methoxypropyloxy)-benzyl bromide in 500 ml of tetrahydrofuran is added dropwise. The temperature of the reaction mixture is allowed to rise from -70° to 0°C over a period of 2 hours. The reaction mixture is left to stand for a further 18 hours at 4°C and then, with stirring, 250 ml of saturated ammonium chloride solution are added. The tetrahydrofuran is evaporated off and the residue is extracted with ethyl acetate. The title compound is obtained from the residue of the extracts by purification by means of FC (2.4 kg of silica gel, ethyl acetate/hexane=1:1):  $R_f$  (ethyl acetate/hexane=1:2)=0.30; m.p. 55°-56°C.

m) 4-Methoxy-3-(3-methoxypropyloxy)-benzyl bromide

97 ml of trimethylbromosilane are added, with stirring at room temperature, to 113.1 g of 4-methoxy-3-(3-methoxypropyloxy)-benzyl alcohol in 1.31 liters of chloroform. After 10 minutes the solvent is evaporated off and the residue is immediately purified by means of FC (900 g of silica gel,

eluant: ethyl acetate/hexane 1:3). The title compound is obtained:  $R_f$  (ethyl acetate/hexane=1:2)=0.34; m.p. 50°-51 °C.

n) 4-Methoxy-3-(3-methoxypropyloxy)-benzyl alcohol

5 7.7 g of 3-hydroxy-4-methoxy-benzyl alcohol, 10.35 g of potassium carbonate and 12.1 g of 1-bromo-3-methoxy-propane are stirred under reflux in 150 ml of acetone for 3 days. After evaporation of the solvent, water is added to the residue and extraction is carried out with ethyl acetate. After evaporation  
10 of the solvent the title compound is obtained from the organic extracts by means of FC (240 g of silica gel, dichloromethane/methanol=96:4):  $R_f$  (ethyl acetate/hexane=2:1)=0.31.

15 **EXAMPLE 125**

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(3-morpholinopropyl)amide dihydrochloride

20 Analogously to Example 124, the title compound is obtained starting from 120 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(3-morpholinopropyl)amide:  $R_f$  (dichloromethane/methanol/conc. ammonia=350:50:1)=0.12; HPLC  $R_t$   
25 =9.64 minutes; FAB-MS (M+H)<sup>+</sup>=580.

The starting material is prepared analogously to Example 124 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine  
30 (Example 124 c) and 4-(3-aminopropyl)morpholine.

**EXAMPLE 126**



5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2,2-dimethyl-2-morpholino-ethyl)amide dihydrochloride

5 Analogously to Example 124, the title compound is obtained starting from 110 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S)-7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2,2-dimethyl-2-morpholino-ethyl)amide:  $R_f$  (dichloromethane/methanol=9:1)=0.05; HPLC  $R_t$   
10 =10.35 minutes; FAB-MS  $(M+H)^+ = 594$ .

The starting material is prepared analogously to Example 124 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine  
15 (Example 124 c) and 4-(2-amino-1,1-dimethyl-ethyl)-morpholine.

a) 4-(2-Amino-1,1-dimethyl-ethyl)-morpholine

A solution of 8.33 g of 2-methyl-2-morpholino-propionic  
20 acid amide in 50 ml of tetrahydrofuran is slowly added at room temperature to 3.33 g of lithium aluminium hydride in 85 ml of tetrahydrofuran. The reaction mixture is then stirred for a further 2 hours under reflux. The reaction mixture is cooled and then 5 ml of water, 6.67 ml of 2 N sodium hydroxide and a  
25 further 5 ml of water are added in succession. The suspension is clarified by filtration and the crude title compound is obtained from the concentrated filtrate:  $^1H$  NMR ( $CDCl_3$ ),  $\delta$ (ppm)=3.67 (4H, m), 2.52 (2H, s), 2.48 (4H, m), 1.37 (2H, bs), 0.92 (6H, s).

30 b) 2-Methyl-2-morpholino-propionic acid amide

272 ml of concentrated sulfuric acid are slowly added, with stirring, to 57.9 g of 2-methyl-2-morpholino-propionitrile (exothermic reaction). After the addition of 43 ml of water, the

mixture is stirred for 2 hours at 100°-110°C. The reaction mixture is cooled to 50°C and added dropwise at 0°C to a solution of 846 ml of 20% ammonia in 242 ml of water. The mixture is then extracted repeatedly with dichloromethane. The organic phases are washed with saturated sodium chloride solution and with sodium sulfate. The crude title compound is obtained from the concentrated filtrate: <sup>1</sup>H NMR (CDCl<sub>3</sub>), δ(ppm)=7.08 (1H, bs), 5.38 (1H, bs), 3.72 (4H, m), 2.53 (4H, m), 1.22 (6H, s)

#### EXAMPLE 127

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-thiomorpholinoethyl)amide dihydrochloride

Analogously to Example 124, the title compound is obtained starting from 110 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-thiomorpholinoethyl)amide: R<sub>f</sub> (dichloromethane/methanol=8:2)=0.33; HPLC R<sub>t</sub> =10.39 minutes; FAB-MS (M+H)<sup>+</sup> =582.

The starting material is prepared analogously to Example 124 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-ox azolidine (Example 124 c) and 4-(2-aminoethyl)thiomorpholine.

#### EXAMPLE 128

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(1,1-dimethyl-2-morpholino-ethyl)amide dihydrochloride

Analogously to Example 124, the title compound is obtained starting from 95 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(1,1-dimethyl-2-morpholino-ethyl)amide:  $R_f$  (dichloromethane/methanol=8:2)=0.42; HPLC  $R_t$  =10.37 minutes; FAB-MS  $(M+H)^+$  =594.

The starting material is prepared analogously to Example 124 a) and 130 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 4-(2-amino-2,2-dimethyl-ethyl)-morpholine.

#### EXAMPLE 129

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[1(R,S)-methyl-2-morpholino-ethyl]amide dihydrochloride

Analogously to Example 124, the title compound is obtained starting from 73 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[1(R,S)-methyl-2-morpholino-ethyl]amide:  $R_f$  (dichloromethane/methanol=8:2)=0.43; HPLC  $R_t$  =9.98/10.58 minutes; FAB-MS  $(M+H)^+$  =580.

The starting material is prepared analogously to Example 124 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 4-(2-amino-2(R,S)-methyl-ethyl)-morpholine.

#### EXAMPLE 130

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1-carbamoyl-1-methyl-ethyl)]-amide hydrochloride

5 1.5 ml of trifluoroacetic acid are added to 56 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S)-7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1-carbamoyl-1-methyl-ethyl)]-amide in 1.5 ml of dichloromethane at 0°C. The mixture is stirred for a further 30 minutes at 0°C. The  
10 reaction mixture is poured onto cooled 1N sodium hydroxide and the product is extracted repeatedly with dichloromethane. The organic phases are dried, and ethereal hydrochloric acid is added. Concentration by evaporation yields the title compound:  
R<sub>f</sub> (dichloromethane/methanol=8:2)=0.30; HPLC R<sub>t</sub> =11.25; FAB-MS  
15 (M+H)<sup>+</sup> =538.

The starting materials are prepared as follows:

a) 5(S)-Tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-  
20 diisopropyl-8-4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1-carbamoyl-1-methyl-ethyl)]-amide

5 mg of p-toluenesulfonic acid (monohydrate) are added to 82 mg of 3-tert-butoxycarbonyl-5(S)-{2-[N-(1-carbamoyl-1-methyl-ethyl)-carbamoyl]-2(S)-isopropyl-ethyl}-4(S)-{2(S)-isopropyl-3-  
25 [4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine in 5 ml of methanol at 0°C. The reaction solution is stirred for a further 18 hours at room temperature. After evaporation of the solvent, 20 ml of saturated sodium hydrogen carbonate solution are added to the residue and  
30 extraction is carried out repeatedly with ethyl acetate. The organic extracts are concentrated by evaporation and purified by means of FC (35 g of silica gel, dichloromethane/methanol=9:1).

The title compound is obtained:  $R_f$   
(dichloromethane/methanol=9:1)=0.47.

b) 3-Tert-butoxycarbonyl-5(S)-{2-[N-(1-carbamoyl-1-methyl-ethyl)-carbamoyl]-2(S)-isopropyl-ethyl}-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine

106  $\mu$ l of 4-methyl-morpholine, 66 mg of 2-aminoisobutyric acid amide hydrochloride and 91 mg of O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) are added in succession to 119 mg of 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124c) in 8 ml of dimethylformamide. The reaction mixture is stirred for 8 days at 40°C. The mixture is concentrated by evaporation and the residue is partitioned between ethyl acetate and saturated sodium chloride solution. The organic phases are concentrated by evaporation and the residue is purified by means of FC (60 g of silica gel, dichloromethane/methanol=95:5). The title compound is obtained:  $R_f$  (dichloromethane/methanol=95:5)=0.30.

#### EXAMPLE 131

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[3-(N-methylcarbamoyl)-propyl]}-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 101 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[3-(N-methylcarbamoyl)-propyl]}-amide:  $R_f$

(dichloromethane/methanol=8:2)=0.32; HPLC  $R_t$  =10.11 minutes;  
FAB-MS (M+H)<sup>+</sup> =552.

The starting material is prepared analogously to Examples  
130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-  
3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-  
methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine  
(Example 124 c) and 4-amino-N-methylbutyric acid amide  
hydrochloride.

#### EXAMPLE 132

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-  
3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[3-(N,N-  
dimethylcarbamoyl)-propyl]}-amide hydrochloride

The title compound is obtained analogously to Example 124  
starting from 91 mg of 5(S)-tert-butoxycarbonylamino-4(S)-  
hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-  
methoxypropyloxy)-phenyl]-octanoic acid {N-[3-(N,N-  
dimethylcarbamoyl)-propyl]}-amide:  $R_f$   
(dichloromethane/methanol=8:2)=0.36; HPLC  $R_t$  =10.38 minutes;  
FAB-MS (M+H)<sup>+</sup> =566.

The starting material is prepared analogously to Examples  
130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-  
3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-  
methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine  
(Example 124 c) and 4-amino-N,N-dimethylbutyric acid amide  
hydrochloride.

#### EXAMPLE 133

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N,N-dimethylcarbamoyl)ethyl]amide hydrochloride

- 5       The title compound is obtained analogously to Example 124 starting from 87 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N,N-dimethylcarbamoyl)ethyl]-amide:  $R_f$
- 10   (dichloromethane/methanol=8:2)=0.38; HPLC  $R_t$  =10.31 minutes; FAB-MS  $(M+H)^+$  =552.

- The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3-amino-N,N-dimethylpropionic acid amide hydrochloride.

20   **EXAMPLE 134**

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1-carbamoylmethyl)]-amide hydrochloride

- 25       The title compound is obtained analogously to Example 124 starting from 84 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1-carbamoylmethyl)]-amide:  $R_f$  (dichloromethane/methanol=8:2)=0.20; HPLC  $R_t$  =9.73
- 30   minutes; FAB-MS  $(M+H)^+$  =510.

      The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-

3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and glycineamide hydrochloride.

#### 5 EXAMPLE 135

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carbamoylethyl)]-amide hydrochloride

- 10 The title compound is obtained analogously to Example 124 starting from 78 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoylethyl)amide:  $R_f$  (dichloromethane/methanol=8:2)=0.24;  
15 HPLC  $R_t$  =9.87 minutes; FAB-MS  $(M+H)^+ =524$ .

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-[2(S)-carboxy-3-methyl-butyl]-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3-aminopropionic acid amide hydrochloride.

#### EXAMPLE 136

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(3-carbamoylpropyl)amide hydrochloride

- The title compound is obtained analogously to Example 124 starting from 74 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(3-carbamoylpropyl)amide:  $R_f$  (dichloromethane/methanol=9:1)=0.06;  
30 HPLC  $R_t$  =10.27 minutes; FAB-MS  $(M+H)^+ =538$ .



The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 4-aminobutyric acid amide hydrochloride.

**EXAMPLE 137**

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 94 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)amide:  $R_f$  (dichloromethane/methanol=8:2)=0.33; HPLC  $R_t$  =11.26 minutes; FAB-MS  $(M+H)^+$  =552.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3-amino-2,2-dimethylpropionic acid amide hydrochloride.

**EXAMPLE 138**

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2,2-dimethyl-2-(N-methylcarbamoyl)ethyl]amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 87 mg of 5(S)-tert-butoxycarbonylamino-4(S)-

hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2,2-dimethyl-2-(N-methylcarbamoyl)-ethyl]}-amide:  $R_f$

(dichloromethane/methanol=8:2)=0.40; HPLC  $R_t$  =11.69 minutes;

5 FAB-MS  $(M+H)^+ = 566$ .

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3-amino-2,2-dimethyl-N-methylpropionic acid amide hydrochloride.

a) 3-Amino-2,2-dimethyl-N-methylpropionic acid amide  
15 hydrochloride

Analogously to Example 121 a) from 3-benzyloxycarbonylamino-2,2-dimethyl-N-methyl-propionic acid amide.

b) 3-Benzyloxycarbonylamino-2,2-dimethyl-N-methylpropionic  
20 acid amide

4.19 g of 3-benzyloxycarbonylamino-2,2-dimethylpropionic acid ethyl ester and 50 ml of 33% methylamine (in ethanol) are stirred for 8 days at 60°C in a bomb tube. The reaction mixture is concentrated by evaporation and the residue is purified by FC (220 g of silica gel, dichloromethane/methanol=95:5). The title  
25 compound is obtained:  $R_f$  (dichloromethane/methanol=9:1)=0.51.

c) 3-Benzyloxycarbonylamino-2,2-dimethylpropionic acid  
30 ethyl ester

31 ml of 90% chloroformic acid benzyl ester are slowly added, at 0°-5°C., to 29.04 g of 3-amino-2,2-dimethylpropionic acid ethyl ester in 500 ml of ethyl acetate and 250 ml of 1 M

sodium hydrogen carbonate solution. The reaction mixture is stirred for 2 hours at 0°-5°C and extracted with ethyl acetate. The organic phases are washed with saturated sodium chloride solution and then concentrated. The evaporation residue is  
5 purified by FC (1 kg of silica gel; eluant: ethyl acetate/hexane=1:3). The title compound is obtained:  $R_f$  (ethyl acetate/hexane=1:3)=0.28.

**EXAMPLE 139**

10 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N-methylcarbamoyl)ethyl]amide hydrochloride

The title compound is obtained analogously to Example 124  
15 starting from 92 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N-methylcarbamoyl)-ethyl]amide:  $R_f$  (dichloromethane/methanol=8:2)=0.24; HPLC  $R_t$  =10.40 minutes;  
20 FAB-MS  $(M+H)^+ = 538$ .

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine  
25 (Example 124 c) and 3-amino-N-methylpropionic acid amide hydrochloride.

**EXAMPLE 140**

30 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(3-morpholino-3-oxopropyl)amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 99 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(3-morpholino-3-oxopropyl)amide:  $R_f$  (dichloromethane/methanol=8:2)=0.51; HPLC  $R_t$  =11.35 minutes; FAB-MS  $(M+H)^+$  =594.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3-aminopropionic acid morpholide hydrochloride.

#### 15 **EXAMPLE 141**

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoyl-1(R,S)-methyl-ethyl)amide hydrochloride

20 The title compound is obtained analogously to Example 124 starting from 86 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-1(R,S)-methyl-ethyl)]-amide:  $R_f$  (dichloromethane/methanol=8:2)=0.24; 25 HPLC  $R_t$  =10.43/11.16 minutes; FAB-MS  $(M+H)^+$  =538.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3(R,S)-aminobutyric acid amide hydrochloride.

**EXAMPLE 142**

5 (S) -Amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-  
3- (3-methoxypropyloxy) -phenyl] -octanoic acid {N- [2- (N-  
5 methylcarbamoyl) -1 (R,S) -methyl-ethyl] } -amide hydrochloride

The title compound is obtained analogously to Example 124  
starting from 95 mg of 5 (S) -tert-butoxycarbonylamino-4 (S) -  
hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4- methoxy-3- (3-  
10 methoxypropyloxy) -phenyl] -octanoic acid {N- [2- (N-  
methylcarbamoyl) -1 (R,S) -methyl-ethyl] } -amide:  $R_f$   
(dichloromethane/methanol=8:2)=0.33; HPLC  $R_t$  =10.78/11.45  
minutes; FAB-MS (M+H)<sup>+</sup> =552.

15 The starting material is prepared analogously to Examples  
130 a) and 124 b) from 3-tert-butoxycarbonyl-5 (S) - (2 (S) -carboxy-  
3-methyl-butyl) -4 (S) - {2 (S) -isopropyl-3- [4-methoxy-3- (3-  
methoxypropyloxy) -phenyl] -propyl} -2,2-dimethyl-1,3-oxazolidine  
(Example 124 c) and 3 (R,S) -amino-N-methylbutyric acid amide  
20 hydrochloride.

**EXAMPLE 143**

5 (S) -Amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-  
3- (3-methoxypropyloxy) -phenyl] -octanoic acid {N- [2- (N,N-  
25 dimethylcarbamoyl) -1 (R,S) -methyl-ethyl] } -amide hydrochloride

The title compound is obtained analogously to Example 124  
starting from 95 mg of 5 (S) -tert-butoxycarbonylamino-4 (S) -  
hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-  
30 methoxypropyloxy) -phenyl] -octanoic acid {N- [2- (N,N-  
dimethylcarbamoyl) -1 (R,S) -methyl-ethyl] } -amide:  $R_f$   
(dichloromethane/methanol=8:2)=0.39; HPLC  $R_t$  =11.44/12.04  
minutes; FAB-MS (M+H)<sup>+</sup> =566.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3(R,S)-amino-N,N-dimethylbutyric acid amide hydrochloride.

**EXAMPLE 144**

5-(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-1(R)-isopropylethyl)]-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 71 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-1(R)-isopropyl-ethyl)]-amide:  $R_f$  (dichloromethane/methanol=8:2)=0.27; HPLC  $R_t$  =10.64 minutes; FAB-MS  $(M+H)^+$  =566.

20

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3(S)-amino-4-methyl-pentanoic acid amide hydrochloride.

a) 3(S)-Amino-4-methylpentanoic acid amide hydrochloride is prepared analogously to Example 121 a from 3(R)-benzyloxycarbonylamino-4-methyl-pentanoic acid amide.

30

b) 3(S)-Benzyloxycarbonylamino-4-methylpentanoic acid amide

2.23 g of 3(S)-benzyloxycarbonylamino-4-methylpentanoic acid ethyl ester and 50 ml of 6 N ammonia (in methanol) are stirred for 6 days at 75°C in a bomb tube. The reaction mixture is concentrated by evaporation and the residue is crystallised from ethyl acetate. The title compound is obtained:  $R_f$  (dichloromethane/methanol=95:5)=0.20; m.p. 171°-172°C.

**EXAMPLE 145**

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(N-methylcarbamoyl)-1(R)-isopropyl-ethyl]}-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 81 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N-methylcarbamoyl)-1(R)-isopropyl-ethyl]amide:  $R_f$  (dichloromethane/methanol=8:2)=0.37; HPLC  $R_t$  =10.96 minutes; FAB-MS (M+H)<sup>+</sup> =580.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3(R)-amino-4-methyl-pentanoic acid N-(methyl)amide hydrochloride.

a) 3(R)-Amino-4-methylpentanoic acid N-(methyl)amide hydrochloride is prepared analogously to Example 121 a) from 3(R)-benzyloxycarbonylamino-4-methyl-pentanoic acid N-(methyl)amide.

b) 3(R)-Benzyloxycarbonylamino-4-methylpentanoic acid N-(methyl)amide

2.23 g of 3(R)-benzyloxycarbonylamino-4-methylpentanoic acid ethyl ester and 50 ml of 33% methylamine (in ethanol) are left to stand for 48 hours at room temperature. The reaction mixture is concentrated by evaporation and the residue is crystallised from ethyl acetate. The title compound is obtained:  $R_f$  (dichloromethane/methanol=95:5)=0.24; m.p. 190°-191°C.

#### EXAMPLE 146

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(N,N-dimethylcarbamoyl)-1(R)-isopropyl-ethyl]}-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 72 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(N,N-dimethylcarbamoyl)-1(R)-isopropyl-ethyl]}-amide:  $R_f$  (dichloromethane/methanol=8:2)=0.45; HPLC  $R_t$  =11.76 minutes; FAB-MS (M+H)<sup>+</sup> =594.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3(R)-amino-4-methyl-pentanoic acid N,N-dimethylamide hydrochloride.

a) 3(R)-Amino-4-methylpentanoic acid N,N-dimethylamide hydrochloride is prepared analogously to Example 121 a) from



3 (R) -benzyloxycarbonylamino-4-methyl-pentanoic acid N,N-dimethylamide.

5 b) 3 (R) -Benzyloxycarbonylamino-4-methylpentanoic acid N,N-dimethylamide

2.23 g of 3 (R) -benzyloxycarbonylamino-4-methylpentanoic acid ethyl ester and 50 ml of 30% dimethylamine (in methanol) are stirred for 6 days at 75°C in a bomb tube. The reaction mixture is concentrated by evaporation and the residue is  
10 purified by FC (dichloromethane/methanol=97:3). The title compound is obtained:  $R_f$  (dichloromethane/methanol=95:5)=0.40.

#### EXAMPLE 147

5 (S) -Amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-  
15 3- (3-methoxypropyloxy) -phenyl] -octanoic acid [N- (1 (S) -carbamoyl-2-hydroxy-ethyl)] -amide hydrochloride

The title compound is obtained analogously to Example 130 starting from 82 mg of 5 (S) -tert-butoxycarbonylamino-4 (S) -  
20 hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxypropyloxy) -phenyl] -octanoic acid [N- (1 (S) -carbamoyl-2-hydroxy-ethyl)] -amide:  $R_f$  (dichloromethane/methanol=8:2)=0.16; HPLC  $R_t$  =10.09 minutes; FAB-MS  $(M+H)^+$  =540.

25 The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5 (S) - (2 (S) -carboxy-3-methyl-butyl) -4 (S) - {2 (S) -isopropyl-3- [4-methoxy-3- (3-methoxypropyloxy) -phenyl] -propyl} -2,2-dimethyl-1,3-oxazolidine (Example 124 c) and L-serine amide hydrochloride.

30

#### EXAMPLE 148

5 (S)-Amino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1 (S), 2-dicarbamoyl-ethyl)]-amide hydrochloride

5 The title compound is obtained analogously to Example 130 starting from 68 mg of 5 (S)-tert-butoxycarbonylamino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1 (S), 2-dicarbamoyl-ethyl)]-amide:  $R_f$  (dichloromethane/methanol=8:2)=0.12; HPLC  $R_t$   
10 =9.54 minutes; FAB-MS  $(M+H)^+ =567$ .

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5 (S)- (2 (S)-carboxy-3-methyl-butyl)-4 (S)-{2 (S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine  
15 (Example 124 c) and L-aspartic acid diamide hydrochloride.

#### EXAMPLE 149

5 (S)-Amino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1 (S), 3-dicarbamoylpropyl)]-amide hydrochloride  
20

The title compound is obtained analogously to Example 130 starting from 83 mg of 5 (S)-tert-butoxycarbonylamino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1 (S), 3-dicarbamoylpropyl)]-amide:  $R_f$   
25 (dichloromethane/methanol=8:2)=0.13; HPLC  $R_t$  =9.50 minutes; FAB-MS  $(M+H)^+ =581$ .

30

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5 (S)- (2 (S)-carboxy-3-methyl-butyl)-4 (S)-{2 (S)-isopropyl-3-[4-methoxy-3-(3-

methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine  
(Example 124 c) and L-glutaric acid diamide hydrochloride.

**EXAMPLE 150**

5           5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-  
3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1(S)-  
carbamoylpropyl)]-amide hydrochloride

10           The title compound is obtained analogously to Example 130  
starting from 90 mg of 5(S)-tert-butoxycarbonylamino-4(S)-  
hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-  
methoxypropyloxy)-phenyl]-octanoic acid [N-(1(S)-  
carbamoylpropyl)]-amide:  $R_f$  (dichloromethane/methanol=8:2)=0.30;  
HPLC  $R_t$  =10.73 minutes; FAB-MS  $(M+H)^+$  =538.

15

          The starting material is prepared analogously to Examples  
130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-  
3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-  
methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine  
20 (Example 124 c) and 2(S)-aminobutyric acid amide hydrochloride.

**EXAMPLE 151**

          5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-  
3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1(S)-carbamoyl-  
25 2(S)-methyl-butyl)]-amide hydrochloride

          The title compound is obtained analogously to Example 130  
starting from 73 mg of 5(S)-tert-butoxycarbonylamino-4(S)-  
hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-  
30 methoxypropyloxy)-phenyl]-octanoic acid [N-(1(S)-carbamoyl-2(S)-  
methyl-butyl)]-amide:  $R_f$  (dichloromethane/methanol=8:2)=0.36;  
HPLC  $R_t$  =11.59 minutes; FAB-MS  $(M+H)^+$  =566.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and L-isoleucine amide hydrochloride.

**EXAMPLE 152**

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2(R,S)-carbamoyl-2(R,S)-methyl-ethyl]-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 93 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2(R,S)-carbamoyl-2(R,S)-methyl-ethyl]-amide:  $R_f$  (dichloromethane/methanol=8:2)=0.28; HPLC  $R_t$  =10.19/10.31 minutes; FAB-MS  $(M+H)^+$  =538.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3-amino-2(R,S)-methylpropionic acid amide hydrochloride.

**EXAMPLE 153**

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2(R,S)-(N-methylcarbamoyl)-2(R,S)-methyl-ethyl]-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 93 mg of 5(S)-tert-butoxycarbonylamino-4(S)-

hydroxy-2(S), 7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2(R,S)-(N-methylcarbamoyl)-2(R,S)-methyl-ethyl]amide:  $R_f$  (dichloromethane/methanol=8:2)=0.31; HPLC  $R_t$  =10.76/10.85 minutes; FAB-MS (M+H)<sup>+</sup> =552.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3-amino-2(R,S)-methylpropionic acid N-methylamide hydrochloride.

a) 3-Amino-2(R,S)-methylpropionic acid N-methylamide hydrochloride is prepared analogously to Example 121 a) from 3-benzyloxycarbonylamino-2(R,S)-methylpropionic acid N-methylamide.

b) 3-Benzyloxycarbonylamino-2(R,S)-methylpropionic acid N-methylamide

2.52 g of 3-benzyloxycarbonylamino-2(R,S)-methylpropionic acid methyl ester and 50 ml of 33% methylamine (in ethanol) are stirred at room temperature for 48 hours. The reaction mixture is concentrated by evaporation and the title compound is obtained from the residue by crystallisation from ethyl acetate:  $R_f$  (dichloromethane/methanol=95:5)=0.42; m.p. 128°129°C.

c) 3-Benzyloxycarbonylamino-2(R,S)-methylpropionic acid methyl ester

22.6 g of 3-benzyloxycarbonylamino-2(R,S)-methylpropionic acid are left to stand for 24 hours in 230 ml of methanol with a few drops of concentrated sulfuric acid. The reaction mixture is concentrated by evaporation and the residue is purified by FC

(220 g of silica gel, dichloromethane). The title compound is obtained:  $R_f$  (dichloromethane/methanol=95:5)=0.60.

d) 3-Benzoyloxycarbonylamino-2(R,S)-methylpropionic acid

5 A solution of 41.7 ml of chloroformic acid benzyl ester (9%) in toluene is added to 25 g of 3-amino-2(R,S)-methylpropionic acid in 533 ml of 1 N sodium hydroxide at 0°C. The reaction mixture is then stirred for 30 minutes at 0°C. After the addition of 400 ml of diethyl ether, the aqueous phase  
10 is removed and 140 ml of 4 N hydrochloric acid are added. The crude title compound is obtained from the organic phase by extraction with diethyl ether:  $R_f$  (dichloromethane/methanol=8:2)=0.41.

15 **EXAMPLE 154**

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-1(S)-methyl-ethyl)]-amide hydrochloride

20 The title compound is obtained analogously to Example 124 starting from 445 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-1(S)-methyl-ethyl)]-amide:  $R_f$  (dichloromethane/methanol=8:2)=0.24;  
25 HPLC  $R_t$  =10.27 minutes; FAB-MS  $(M+H)^+$  =538.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine  
30 (Example 124 c) and 3(S)-aminobutyric acid amide hydrochloride.

**EXAMPLE 155**

5 (S)-Amino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-1 (R)-methyl-ethyl)]-amide hydrochloride

5 The title compound is obtained analogously to Example 124 starting from 110 mg of 5 (S)-tert-butoxycarbonylamino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carbamoyl-1 (R)-methyl-ethyl)]-amide:  $R_f$  (dichloromethane/methanol=8:2)=0.24;  
10 HPLC  $R_t$  =10.92 minutes; FAB-MS  $(M+H)^+ =538$ .

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5 (S)-(2 (S)-carboxy-3-methyl-butyl)-4 (S)-{2 (S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine  
15 (Example 124 c) and 3 (R)-aminobutyric acid amide hydrochloride.

#### EXAMPLE 156

5 (S)-Amino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2 (S)-carbamoyl-2 (S)-methyl-ethyl]-amide hydrochloride  
20

The title compound is obtained analogously to Example 124 starting from 350 mg of 5 (S)-tert-butoxycarbonylamino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2 (S)-carbamoyl-2 (S)-methyl-ethyl]-amide (diastereoisomer A):  $R_f$  (dichloromethane/methanol=8:2)=0.19; HPLC  $R_t$  =10.50 minutes;  
25 FAB-MS  $(M+H)^+ =538$ .

30

The starting material is prepared as follows:

5 (S) -Tert-butoxycarbonylamino-4 (S) -hydroxy-2 (S) , 7 (S) -  
diisopropyl-8- [4-methoxy-3- (3-methoxypropyloxy) -phenyl] -octanoic  
acid N- [2 (S) -carbamoyl-2 (S) -methyl-ethyl] -amide (diastereoisomer  
A) and

5 5 (S) -tert-butoxycarbonylamino-4 (S) -hydroxy-2 (S) , 7 (S) -  
diisopropyl-8-4-methoxy-3 (3-methoxypropyloxy) -phenyl] -octanoic  
acid [N- [2 (S) -carbamoyl-2 (R) -methyl-ethyl] -amide  
(diastereoisomer B)

40 mg of p-toluenesulfonic acid (monohydrate) are added to  
10 1.29 g of 3-tert-butoxy-carbonyl-5 (S) - {2- [N- (2-carbamoyl-2 (R, S) -  
methyl-ethyl) -carbamoyl] -2 (S) -isopropyl-ethyl} -4 (S) - {2 (S) -  
isopropyl-3- [4-methoxy-3- (3-methoxypropyloxy) -phenyl] -propyl} -  
2,2-dimethyl-1,3-oxazolidine in 50 ml of methanol at 0°C. The  
reaction solution is stirred for 18 hours at room temperature.  
15 After removal of the solvent by evaporation, 100 ml of saturated  
sodium hydrogen carbonate solution are added to the residue and  
extraction is carried out repeatedly with ethyl acetate. The  
organic extracts are concentrated by evaporation and purified by  
FC (5 times with 60 g of silica gel,  
20 dichloromethane/methanol=9:1). The title compounds are obtained:

Diastereoisomer A:  $R_t$  (dichloromethane/methanol=95:5)=0.19.

Diastereoisomer B:  $R_t$  (dichloromethane/methanol=95:5)=0.14.

25

The starting material is prepared analogously to Example  
124 b) from 3-tert-butoxy-carbonyl-5 (S) - (2 (S) -carboxy-3-methyl-  
butyl) -4 (S) - {2 (S) -isopropyl-3- [4-methoxy-3- (3-methoxypropyloxy) -  
phenyl] -propyl} -2,2-dimethyl-1,3-oxazolidine (Example 124 c) and  
30 3-amino-2 (R, S) -methylpropionic acid amide hydrochloride.

#### EXAMPLE 157



5 (S)-Amino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2 (R)-carbamoyl-2 (R)-methyl-ethyl]-amide hydrochloride

5 The title compound is obtained analogously to Example 124 starting from 370 mg of 5 (S)-tert-butoxycarbonylamino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2 (R)-carbamoyl-2 (R)-methyl-ethyl]-amide diastereoisomer B (Example 156 a)):  $R_t$  (dichloromethane/methanol=8:2)=0.19; HPLC  $R_t$  =10.39 minutes; FAB-MS  $(M+H)^+ = 538$ .

#### EXAMPLE 158

15 5 (S)-Amino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2 (R)-(N-methylcarbamoyl)-2 (R)-methyl-ethyl]}-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 60 mg of 5 (S)-tert-butoxycarbonylamino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2 (R)-(N-methylcarbamoyl)-2 (R)-methyl-ethyl]-amide:  $R_f$  (dichloromethane/methanol=8:2)=0.31; HPLC  $R_t$  =10.33 minutes; FAB-MS  $(M+H)^+ = 552$ .

25 The starting material is prepared analogously to Example 130 a) from 3-tert-butoxy-carbonyl-5 (S)-{2-[N-(2 (R)-(N-methylcarbamoyl)-2 (R)-methyl-ethyl)-carbamoyl]-2 (S)-isopropyl-ethyl}-4 (S)-{2 (S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine.

a) 3-Tert-butoxycarbonyl-5 (S)-{2 (S)-[N-(2 (R)-(N-methylcarbamoyl)-2 (R)-methyl-ethyl)-carbamoyl]-2 (S)-isopropyl-

ethyl}-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine

120 mg of 3-tert-butoxycarbonyl-5(S)-{2(S)-[N-(2(R)-methoxycarbonyl)-2(R)-methyl-ethyl)-carbamoyl]-2(S)-isopropyl-ethyl}-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine are left to stand for 48 hours at room temperature in 5 ml of 33% methylamine solution (in ethanol). The reaction mixture is concentrated by evaporation and the residue is purified by FC (30 g of silica gel, dichloromethane/methanol=95:5). The title compound is obtained:  $R_f$  (dichloromethane/methanol=95:5)=0.30.

b) 3-Tert-butoxycarbonyl-5(S)-{2(S)-[N-(2(R)-methoxycarbonyl)-2(R)-methyl-ethyl)-carbamoyl]-2(S)-isopropyl-ethyl}-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine

The title compound is prepared analogously to Example 124 b) from 3-tert-butoxy-carbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3-amino-2(R)-methylpropionic acid methyl ester hydrochloride.

c) 3-Amino-2(R)-methylpropionic acid methyl ester hydrochloride

2.7 g of 3-azido-2(R)-methylpropionic acid methyl ester are hydrogenated in the presence of 1.4 g of 10% Pd/C in 50 ml of tetrahydrofuran for 4 hours at room temperature at pH 6.0 (pH-stat; 2 N hydrochloric acid). The reaction mixture is filtered and concentrated by evaporation. The title compound is obtained by crystallisation from isopropanol/diethyl ether:  $^1\text{H}$  NMR (DMSO- $d_6$ ),  $\delta$ (ppm)=7.95(3H, bs), 3.65(3H, s), 3.12-2.78 (3H, m), 1.15 (3H, d); m.p. 122°-125°C.

**EXAMPLE 159**

5 (S)-Amino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2 (S)-(N-methylcarbamoyl)-2 (S)-methyl-ethyl]}-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 81 mg of 5 (S)-tert-butoxycarbonylamino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2 (S)-(N-methylcarbamoyl)-2 (S)-methyl-ethyl]}-amide:  $R_f$  (dichloromethane/methanol=8:2)=0.31; HPLC  $R_t$  =10.50 minutes; FAB-MS  $(M+H)^+$  =552.

15 The starting material is prepared analogously to Example 158 a) to c) from 3-tert-butoxy-carbonyl-5 (S)-(2 (S)-carboxy-3-methyl-butyl)-4 (S)-{2 (S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3-amino-2 (S)-methylpropionic acid methyl ester hydrochloride.

**EXAMPLE 160**

5 (S)-Amino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carboxy-2,2-dimethyl-ethyl)]-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 71 mg of 5 (S)-tert-butoxycarbonylamino-4 (S)-hydroxy-2 (S), 7 (S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carboxy-2,2-dimethyl-ethyl)]-amide:  $R_f$  (dichloromethane/methanol=8:2)=0.52; HPLC  $R_t$  =10.95 minutes; FAB-MS  $(M+H)^+$  =553.

The starting material is prepared analogously to Example 130 a) from 3-tert-butoxy-carbonyl-5(S)-{2(S)-[N-(2-carboxy-2,2-dimethyl-ethyl)-carbamoyl]-2(S)-isopropyl-ethyl}-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine.

a) 3-Tert-butoxycarbonyl-5(S)-{2(S)-[N-(2-carboxy-2,2-dimethyl-ethyl)-carbamoyl]-2(S)-isopropyl-ethyl}-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine

36 mg of 3-tert-butoxycarbonyl-5(S)-{2(S)-[N-(2-ethyloxycarbonyl-2,2-dimethyl-ethyl)-carbamoyl]-2(S)-isopropyl-ethyl}-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine are stirred for 24 hours at room temperature in 1 ml of ethanol and 0.1 ml of 2N potassium hydroxide. The reaction mixture is concentrated by evaporation and, after the addition of 0.1 ml of 2N hydrochloric acid, extracted repeatedly with diethyl ether. The extracts are concentrated by evaporation and purified by FC (18 g of silica gel, dichloromethane/methanol=9:1). The title compound is obtained:  $R_f$  (dichloromethane/methanol=9:1)=0.45.

The starting material is prepared analogously to Example 124 b) from 3-tert-butoxy-carbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 3-amino-2,2-dimethylpropionic acid ethyl ester.

#### EXAMPLE 161

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carboxy-2,2-diethyl-ethyl)]-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 136 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(2-carboxy-2,2-diethyl-ethyl)]-amide:  $R_f$  (dichloromethane/methanol=8:2)=0.26; HPLC  $R_t$  =12.53 minutes; FAB-MS  $(M+H)^+ =581$ .

The starting material is prepared analogously to Example 130 a) from 3-tert-butoxy-carbonyl-5(S)-{2(S)-[N-(2-carboxy-2,2-diethyl-ethyl)-carbamoyl]-2(S)-isopropyl-ethyl}-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine.

a) 3-Tert-butoxycarbonyl-5(S)-{2-N-(2-carboxy-2,2-diethyl-ethyl)-carbamoyl]-2(S)-isopropyl-ethyl}-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine

258 mg of 3-tert-butoxycarbonyl-5(S)-{2-[N-(2-(2-ethyloxycarbonyl-2,2-diethyl-ethyl)-carbamoyl]-2(S)-isopropyl-ethyl}-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine are stirred for 24 hours at 80°C. in 6 ml of ethanol and 0.69 ml of 2 N potassium hydroxide. The reaction mixture is concentrated by evaporation and, after the addition of 0.69 ml of 2 N hydrochloric acid, extracted repeatedly with diethyl ether. The extracts are concentrated by evaporation and purified by FC (35 g of silica gel, dichloromethane/methanol=9:1). The title compound is obtained:  $R_f$  (dichloromethane/methanol=9:1)=0.50.

The starting material is prepared analogously to Example 124 b) from 3-tert-butoxy-carbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and

3-amino-2,2-diethylpropionic acid ethyl ester.

**EXAMPLE 162**

5 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[(1-carboxycyclopentyl)-methyl]-amide hydrochloride

10 The title compound is obtained analogously to Example 124 starting from 142 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[(1-carboxycyclopentyl)-methyl]-amide:  $R_f$  (dichloromethane/methanol=8:2)=0.26; HPLC  $R_t$  =12.18 minutes; FAB-MS  $(M+H)^+ =579$ .

15

The starting material is prepared analogously to Examples 130 a), 161 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 1-(aminomethyl)cyclopentane-1-carboxylic acid ethyl ester.

20

**EXAMPLE 163**

25 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(1H-tetrazol-5-yl)-ethyl]}-amide hydrochloride

30 The title compound is obtained analogously to Example 124 starting from 100 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[2-(1H-tetrazol-5-yl)-ethyl]}-amide:  $R_f$  (dichloromethane/methanol=8:2)=0.19; HPLC  $R_t$  =12.30 minutes; FAB-MS  $(M+H)^+ =549$ .

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 2-(1H-tetrazol-5-yl)-ethylamine.

**EXAMPLE 164**

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[1(S)-(5-oxopyrrolidin-2-yl)methyl]-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 100 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S)-7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[(1-carboxycyclopentyl)-methyl]-amide:  $R_f$  (dichloromethane/methanol=8:2)=0.27; HPLC  $R_t$  =12.55 minutes; FAB-MS  $(M+H)^+ =550$ .

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 5(S)-(aminomethyl)-2-pyrrolidone.

**EXAMPLE 165**

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[1(R)-(5-oxopyrrolidin-2-yl)methyl]-amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 95 mg of 5(S)-tert-butoxycarbonylamino-4(S)-

hydroxy-2(S), 7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[1(R)-(5-oxopyrrolidin-2-yl)methyl]-amide:  $R_f$  (dichloromethane/methanol=8:2)=0.31; HPLC  $R_t$  =12.24 minutes;

5 FAB-MS  $(M+H)^+ = 550$ .

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 5(R)-(aminomethyl)-2-pyrrolidone.

#### EXAMPLE 166

5(S)-Amino-4(S)-hydroxy-2(S), 7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[(N,N-dimethyl)-carbamoylmethyl]}-amide hydrochloride

The title compound is obtained analogously to Example 130 starting from 56 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S), 7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid {N-[(N,N-dimethyl)-carbamoylmethyl]}-amide and after lyophilisation:  $R_f$  (ethyl acetate/methanol/conc. ammonia=80: 15:5)=0.42; HPLC  $R_t$  =11.82 minutes; FAB-MS  $(M+H)^+ = 538$ .

25

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 2(S)-aminoacetic acid (N,N-dimethyl)-amide hydrochloride.

30

#### EXAMPLE 167



5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[N-(morpholin-4-yl)carbamoylmethyl]amide hydrochloride

5 The title compound is obtained analogously to Example 130 starting from 76 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[N-(morpholin-4-yl)carbamoylmethyl]-amide and after lyophilisation:  $R_t$  (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.43; HPLC  $R_t$  =10.66 minutes; FAB-MS (M+H)<sup>+</sup> =580.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-15 3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 2-aminoacetic acid N-(morpholin-4-yl)amide hydrochloride.

#### 20 **EXAMPLE 168**

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1(S)-carbamoyl-ethyl)]-amide hydrochloride

25 The title compound is obtained analogously to Example 130 starting from 64 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid [N-(1(S)-carbamoylethyl)]-amide and after lyophilisation:  $R_f$  (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.42; HPLC  $R_t$  =10.48 minutes; FAB-MS (M+H)<sup>+</sup> =524.

The starting material is prepared analogously to Examples 130 a) and 130 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 2(S)-aminopropionic acid amide hydrochloride.

**EXAMPLE 169**

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-{1(S)-[(N-methyl)-carbamoyl]-ethyl}-amide hydrochloride

The title compound is obtained analogously to Example 130 starting from 31 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-{1(S)-[(N-methyl)-carbamoyl]-ethyl}-amide and after lyophilisation:  $R_f$  (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.38; HPLC  $R_t$  =11.08 minutes; FAB-MS  $(M+H)^+$  =538.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 2(S)-aminopropionic acid (N-methyl)-amide hydrochloride.

**EXAMPLE 170**

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-{1(S)-[(N,N-dimethyl)-carbamoyl]-ethyl}-amide hydrochloride

The title compound is obtained analogously to Example 130 starting from 86 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-{1(S)-[(N,N-dimethyl)-carbamoyl]-ethyl}-amide and after lyophilisation:  $R_f$  (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.50; HPLC  $R_t$  =11.53 minutes; FAB-MS (M+H)<sup>+</sup> =552.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 2(S)-aminopropionic acid (N,N-dimethyl)-amide hydrochloride.

#### EXAMPLE 171

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-{1(S)-N-[(morpholin-4-yl)-carbamoyl]-ethyl}amide hydrochloride

The title compound is obtained analogously to Example 130 starting from 51 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-{1(S)-N-[(morpholin-4-yl)-carbamoyl]-ethyl}amide and after lyophilisation:  $R_f$  (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.51; HPLC  $R_t$  =11.29 minutes; FAB-MS (M+H)<sup>+</sup> =594.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 2(S)-aminopropionic acid N-(morpholin-4-

yl)amide hydrochloride.

**EXAMPLE 172**

5 (S) -Amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-  
5 3- (3-methoxypropyloxy) -phenyl] -octanoic acid N- [1 (S) -carbamoyl-  
butyl]amide hydrochloride

The title compound is obtained analogously to Example 130  
starting from 49 mg of 5 (S) -tert-butoxycarbonylamino-4 (S) -  
10 hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-  
methoxypropyloxy) -phenyl] -octanoic acid N- [1 (S) -  
carbamoylbutyl]amide and after lyophilisation:  $R_t$  (ethyl  
acetate)=0.38; HPLC  $R_t$  =10.67 minutes; FAB-MS  $(M+H)^+$  =552.

The starting material is prepared analogously to Example  
15 130 a) and 130 b) from 3-tert-butoxycarbonyl-5 (S) - (2 (S) -carboxy-  
3-methyl-butyl) -4 (S) - {2 (S) -isopropyl-3- [4-methoxy-3- (3-  
methoxypropyloxy) -phenyl] -propyl} -2,2-dimethyl-1,3-oxazolidine  
(Example 124 c) and 2 (S) -aminopentanoic acid amide  
hydrochloride.

20

**EXAMPLE 173**

5 (S) -Amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-  
3- (3-methoxypropyloxy) -phenyl] -octanoic acid N- [1 (S) -carbamoyl-  
2-methyl-propyl] -amide hydrochloride

25

The title compound is obtained analogously to Example 130  
starting from 65 mg of 5 (S) -tert-butoxycarbonylamino-4 (S) -  
hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-  
methoxypropyloxy) -phenyl] -octanoic acid N- [1 (S) -carbamoyl-2-  
30 methyl-propyl] -amide and after lyophilisation:  $R_t$  (ethyl  
acetate/methanol/conc. ammonia=80: 15:5)=0.47; HPLC  $R_t$  =11.22  
minutes; FAB-MS  $(M+H)^+$  =552.

The starting material is prepared analogously to Example 130 a) and 130 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 2(S)-amino-3-methylbutyric acid amide hydrochloride.

**EXAMPLE 174**

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[1(S):(N-methylcarbamoyl)-2-methyl-propyl]amide hydrochloride

The title compound is obtained analogously to Example 130 starting from 58 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[1(S)-(N-methylcarbamoyl)-2-methyl-propyl]amide and after lyophilisation:  $R_f$  (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.51; HPLC  $R_t$  =11.87 minutes; FAB-MS  $(M+H)^+ = 566$ .

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-ox azolidine (Example 124 c) and 2(S)-amino-3-methylbutyric acid (N-methyl)amide hydrochloride.

**EXAMPLE 175**

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[1(S)-(N,N-dimethylcarbamoyl)-2-methyl-propyl]amide hydrochloride

The title compound is obtained analogously to Example 130 starting from 80 mg of 5(S)-tert-butoxy carbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[1(S)-(N,N-dimethylcarbamoyl)-2-methyl-propyl]amide and after lyophilisation:  $R_f$  (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.62; HPLC  $R_t$  =12.36 minutes; FAB-MS (M+H)<sup>+</sup> =580.

10 The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 2(S)-amino-3-methylbutyric acid (N,N-dimethyl)amide hydrochloride.

The starting material is prepared as follows:

a) 2(S)-Amino-3-methylbutyric acid (N,N-dimethyl)amide hydrochloride

20 0.85 g of 2(S)-tert-butoxycarbonylamino-3-methylbutanoic acid (N,N-dimethyl)amide is dissolved in 10 ml of 4 N hydrochloric acid in dioxane at 0°C and stirred for 7 hours at 0°C. The reaction mixture is lyophilised and the title compound is obtained:  $R_f$  (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.23.

#### EXAMPLE 176

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-{1(S)-[N-(morpholin-4-yl)carbamoyl]-2-methyl-propyl}amide hydrochloride

The title compound is obtained analogously to Example 130 starting from 74 mg of 5(S)-tert-butoxycarbonylamino-4(S)-

hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-{1(S)-[N-(morpholin-4-yl)carbamoyl]-2-methyl-propyl}amide and after lyophilisation:  $R_f$  (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.59; HPLC  $R_t$   
5 =11.81 minutes; FAB-MS  $(M+H)^+ =622$ .

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine  
10 (Example 124 c) and 2(S)-amino-3-methylbutanoic acid N-(morpholin-4-yl)amide hydrochloride.

**EXAMPLE 177**

15 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N-methylsulfonyl)ethyl]amide hydrochloride

The title compound is obtained analogously to Example 124  
20 starting from 90 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N-methylsulfonyl)ethyl]amide and after lyophilisation:  $R_f$  (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.52; HPLC  $R_t$  =11.50  
25 minutes; FAB-MS  $(M+H)^+ =574$ .

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine  
30 (Example 124 c) and 2-aminoethyl-(N-methyl)-sulfonamide.

**EXAMPLE 178**

5 (S) -Amino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxypropyloxy) -phenyl] -octanoic acid N- {2- [N- (morpholin-4-yl) -sulfonyl] ethyl} -amide hydrochloride

5       The title compound is obtained analogously to Example 130 starting from 98 mg of 5 (S) -tert-butoxycarbonylamino-4 (S) -hydroxy-2 (S) , 7 (S) -diisopropyl-8- [4-methoxy-3- (3-methoxypropyloxy) -phenyl] -octanoic acid N- {2- [N- (morpholin-4-yl) -sulfonyl] ethyl} -amide and after lyophilisation:  $R_f$  (ethyl acetate/methanol/conc. ammonia=80: 15:5)=0.53; HPLC  $R_t$  =11.63 minutes; FAB-MS  $(M+H)^+ =630$ .

15       The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5 (S) - (2 (S) -carboxy-3-methyl-butyl) -4 (S) - {2 (S) -isopropyl-3- [4-methoxy-3- (3-methoxypropyloxy) -phenyl] -propyl} -2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 2-aminoethyl-N- (morpholin-4-yl) -sulfonamide.

20       The starting material is prepared as follows:

a) 2-Aminoethyl-N- (morpholin-4-yl) -sulfonamide

3.0 g of 2-phthaloylaminoethyl-N- (morpholin-4-yl) -sulfonamide in 20 ml of methanol are stirred for 2 hours under reflux with 20 ml of hydrazine hydrate. The reaction mixture is cooled and 1.0 ml of concentrated hydrochloric acid and 15 ml of methanol are added. The reaction mixture is filtered and the filtrate is concentrated. After the addition of 10 ml of 10% potassium hydroxide solution the title compound is obtained by extraction with dichloromethane:  $R_f$  (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.26.

b) 2-Phthaloylaminoethyl-N- (morpholin-4-yl) -sulfonamide



4.77 ml of morpholine are added to 5.0 g of 2-phthaloylaminoethylsulfonyl chloride in 40 ml of dichloromethane at -12°C. The reaction mixture is stirred for 30 minutes at 0° and washed with water. The organic phase is dried over sodium sulfate and concentrated. The title compound is obtained:  $R_f$  (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.68.

**EXAMPLE 179**

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N-acetyl)-piperidin-4-yl]ethyl]amide hydrochloride

The title compound is obtained analogously to Example 124 starting from 42 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N-acetyl)-piperidin-4-yl]ethyl]amide and after lyophilisation:  $R_f$  (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.51; HPLC  $R_t$  =12.06 minutes; FAB-MS  $(M+H)^+$  =606.

The starting material is prepared analogously to Examples 130 a) and 124 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 4-(2-aminoethyl)-(N-acetyl)-piperidine hydrochloride.

The starting material is prepared as follows:

a) 4-(2-Aminoethyl)-(N-acetyl)-piperidine hydrochloride is prepared analogously to Example 175 a) from 4-(2-tert-butoxycarbonylaminoethyl)-(N-acetyl)-piperidine.

b) N-Acetyl-4-(2-tert-butoxycarbonylaminoethyl)-piperidine

0.5 g of 4-(2-tert-butoxycarbonylaminoethyl)-piperidine and 0.61 ml of triethylamine are dissolved in 5 ml of dichloromethane and, at 0°C, 0.22 ml of acetyl chloride is added. The reaction mixture is stirred at room temperature for 7 hours and then washed with water. The organic phase is concentrated by evaporation and purified by FC (10 g of silica gel, ethyl acetate/methanol=9:1). The title compound is obtained:  $R_e$  (ethyl acetate/methanol=9:1)=0.39.

10 **EXAMPLE 180**

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[(N-acetyl-piperidin-4-yl)methyl]amide hydrochloride

15 The title compound is obtained analogously to Example 130 starting from 71 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[(N-acetyl-piperidin-4-yl)methyl]amide and after lyophilisation:  $R_t$  (ethyl acetate/methanol/conc. ammonia=80:15:5)=0.44; HPLC  $R_t$  =12.83 minutes; FAB-MS (M+H)<sup>+</sup> =629.

The starting material is prepared analogously to Examples 130 a) and 130 b) from 3-tert-butoxycarbonyl-5(S)-(2(S)-carboxy-3-methyl-butyl)-4(S)-{2(S)-isopropyl-3-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-propyl}-2,2-dimethyl-1,3-oxazolidine (Example 124 c) and 4-aminomethyl-(N-acetyl)-piperidine hydrochloride.

30 **EXAMPLE 181**

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(4-methoxybutyl)-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)amide hydrochloride

The title compound is obtained analogously to Example 105 starting from 25 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(4-methoxybutyl)-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)amide:  
5  $R_f$  (dichloromethane/methanol/conc. ammonia=350:50:1)=0.30; HPLC  $R_t$  =13.31 minutes; FAB-MS  $(M+H)^+$  =550.

The starting material is prepared analogously to Example 82  
10 d), 82 e), Example 83 d), Example 83 and Example 105, except that there is used instead of 4-(3-benzyloxy-propyloxy)-3-(3-methoxypropyloxy)-bromobenzene in Example 82 d), 4-methoxy-3-(4-methoxy-butyl)-bromobenzene, which is prepared as follows:

15 a) 4-Methoxy-3-(4-methoxybutyl)-bromobenzene

A solution of 50 g of 4-methoxy-3-(4-methoxy-2-butenyl)-bromobenzene in 700 ml of tetrahydrofuran is hydrogenated for 2 hours under normal pressure and at room temperature in the presence of 2.5 g of 5% Pt/C. The reaction mixture is filtered.  
20 The filtrate is concentrated by evaporation. The evaporation residue obtained from the filtrate is purified by FC (1.6 kg of silica gel, hexane/ethyl acetate=20:1). Distillation under a high vacuum yields the title compound:  $R_t$  (hexane/ethyl acetate=10:1)=0.38; HPLC  $R_t$  =19.92 minutes; FAB-MS  $(M+H)^+$  =273.

25

b) 4-Methoxy-3-(4-methoxy-2-butenyl)-bromobenzene

25 1.1 g of 3-methoxypropyltriphenylphosphonium bromide are added to a solution, stirred at 5°, of 110.8 g of sodium bis(trimethylsilyl)amide in 1200 ml of tetrahydrofuran. The  
30 reaction mixture is further stirred for 45 minutes at 0° and then a solution of 100 g of 5-bromo-o-anisaldehyde in 1000 ml of tetrahydrofuran is added dropwise thereto. The reaction mixture is stirred for a further 1 hour at 0°. Then, at 0°C, 1 liter of

a saturated ammonium chloride solution is added dropwise. After concentration, the residue is extracted 4 times with ethyl acetate. The organic phases are washed with water and saturated sodium chloride solution and concentrated by evaporation. The  
5 residue is purified by FC (500 g of silica gel, hexane/ethyl acetate=5:1). Distillation under a high vacuum yields the title compound:  $R_f$  (hexane/ethyl acetate=4:1)=0.61.

**EXAMPLE 182**

10 5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-[2-(N,N-dimethylcarbamoyl)ethyl]-amide sodium dihydrogen citrate

768 mg of 5(S)-amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-  
15 [4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-octanoic acid N-[2-(N,N-dimethylcarbamoyl)ethyl]amide hydrochloride (Example 134) are stirred in 50 ml of 0.1 N sodium hydroxide and extracted repeatedly with dichloromethane. The extracts are concentrated and the residue is dissolved in 50 ml of ethanol. 274 mg of  
20 citric acid monohydrate, 50 ml of water and 1.30 ml of 1 N sodium hydroxide are added in succession to the stirred solution. The solution is then concentrated to dryness by evaporation and the residue is taken up in 100 ml of water and lyophilised. The lyophilisate is dissolved in methanol and  
25 clarified by filtration; the filtrate is concentrated and the residue is dried at room temperature under a high vacuum. The title compound is obtained in the form of a white amorphous solid having a melting point of 80°C.

30 **EXAMPLE 183**

5(S)-Amino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(4-methoxybutyl)-phenyl]-octanoic acid N-(2-morpholinoethyl)amide dihydrochloride

The title compound is obtained analogously to Example 124 starting from 100 mg of 5(S)-tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3(4-methoxybutyl)-phenyl]-octanoic acid N-[2-(4-morpholino)ethyl]-amide:  $R_f$  (dichloromethane/methanol=10:1)=0.21; HPLC  $R_t$  =12.69 minutes; FAB-MS  $(M+H)^+ = 564$ .

The starting material is prepared as follows:

a) 5(S)-Tert-butoxycarbonylamino-4(S)-hydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(4-methoxybutyl)-phenyl]-octanoic acid N-[2-(4-morpholino)-ethyl]-amide

10 ml of acetic acid are added to a solution of 100 mg of 3(S)-isopropyl-5(S)-{1(S)-tert-butoxycarbonylamino-3(S)-isopropyl-4-[4-methoxy-3-(4-methoxybutyl)-phenyl]-butyl}-tetrahydrofuran-2-one (for preparation see Example 181) in 2 ml of 4-(2-aminoethyl)morpholine. The reaction mixture is stirred for 39 hours at 80°C and then concentrated by evaporation in a rotary evaporator. Purification of the residue by FC (dichloromethane/methanol=10:1) yields the title compound in the form of a crude product. Crystallisation from diethyl ether/hexane yields the title compound: m.p. -94°-96°C.,  $R_f$  (dichloromethane/methanol=10:1) =0.35; HPLC  $R_t$  =17.42 minutes; FAB-MS  $(M+H)^+ = 664$ .

#### EXAMPLE 184

5(S)-Amino-4(S),8(R,S)-dihydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(2-methoxymethoxyethyl)-phenyl]-octanoic acid (N-butyl)-amide

40 mg of 5(S)-azido-4(S),8(R,S)-dihydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(2-methoxymethoxyethyl)-phenyl]-octanoic acid (N-butyl)-amide are hydrogenated in 10 ml of

methanol/acetic acid (9:1) in the presence of 20 mg of 10% Pd/C at room temperature and under normal pressure. The reaction mixture is filtered and concentrated by evaporation. The residue is purified by FC (2.4 g of silica gel,

5 dichloromethane/methanol=9:1). The title compound is obtained:  $R_f$  (dichloromethane/methanol=9:1)=0.17; HPLC  $R_t$  =11.44 and 12.63 minutes (diastereoisomeric mixture); FAB-MS (M+H)<sup>+</sup>=525.

a) 5(S)-Azido-4(S)-8(R,S)-dihydroxy-2(S)-7(S)-diisopropyl-  
10 8-[4-methoxy-3-(2-methoxy-methoxyethyl)-phenyl]-octanoic acid (N-butyl)-amide

A solution of 400 mg of 3(S)-isopropyl-5(S)-{1(S)-azido-4(R,S)-hydroxy-3(S)-isopropyl-4-[4-methoxy-3-(2-methoxymethoxyethyl)-phenyl]-butyl}-tetrahydrofuran-2-one  
15 (Example 81 d) and 3.8 ml of n-butylamine is stirred for 16 hours at 50°C and then concentrated by evaporation. Purification of the residue by FC (50 g of silica gel, hexane/ethyl acetate=1:1) yields the title compound:  $R_f$  (hexane/ethyl acetate=1:1)=0.44; HPLC  $R_t$  =16.13 and 17.03 minutes  
20 (diastereoisomeric mixture).

#### EXAMPLE 185

5(S)-Amino-4(S),8(S or R)-dihydroxy-2(S),7(S)-diisopropyl-  
8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-  
25 carbamoyl-2,2-dimethyl-ethyl)-amide hydrochloride

60 mg of 5(S)-azido-4(S),8(S or R)-dihydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)-amide and 6 ml of  
30 ethanolamine are hydrogenated in 8 ml of ethanol in the presence of 120 mg of 5% PdO/C for 2 hours at room temperature and under normal pressure. The reaction mixture is filtered and concentrated by evaporation. The residue is dissolved in 0.5 ml

of dioxane and 23 ul of 4N hydrochloric acid in dioxane are added. The title compound is obtained after lyophilisation: HPLC  $R_t$  =10.74; FAB-MS (M+H)<sup>+</sup>=568.

5 The starting materials are prepared as follows:

a) 5(S)-Azido-4(S),8(S or R)-dihydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)-amide

150 mg of 3(S)-isopropyl-5(S)-{1(S)-azido-4(S or R)-hydroxy-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-tetrahydrofuran-2-one (Example 185b) diastereoisomer B) and 109 mg of 3-amino-2,2-dimethylpropionic acid amide are stirred in 3 ml of triethylamine with 30 mg of 2-hydroxypyridine for 24 hours under reflux temperature. After removal of the solvent by evaporation, the residue, in diethyl ether, is washed repeatedly with water. The organic extracts are concentrated by evaporation and purified by FC (10 g of silica gel, dichloromethane/methanol=95:5). The title compound is obtained:  $R_f$  (dichloromethane/methanol=95:5)=0.22; HPLC  $R_t$  =14.88 minutes.

b) 3(S)-Isopropyl-5(S)-{1(S)-azido-4(S or R)-hydroxy-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-tetrahydrofuran-2-one (A) and

25 3(S)-isopropyl-5(S)-{1(S)-azido-4(S or R)-hydroxy-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-tetrahydrofuran-2-one (B)

Separation of 0.5 g of 3(S)-isopropyl-5(S)-{1(S)-azido-4(R,S)-hydroxy-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-tetrahydrofuran-2-one (diastereoisomeric mixture) by means of preparative HPLC on Kromasil 7 C18 (EKA-Nobel, A.B. Sweden); mobile phase: A) water B) acetonitrile, gradient: 20 -80% B in 40 minutes. The two pure

diastereoisomers A and B are obtained (isomer A is eluted first). After concentration of the eluate fractions by evaporation, the aqueous residue is extracted with ethyl acetate. The organic extracts are dried over magnesium sulfate and concentrated. The title compounds are obtained:  
5 diastereoisomer A) HPLC  $R_t$  =18.53 minutes and B) HPLC  $R_t$  =19.49 minutes.

c) 3(S)-Isopropyl-5(S)-1(S)-azido-4(R,S)-hydroxy-3(S)-  
10 isopropyl-4-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-butyl}-tetrahydrofuran-2-one

45.1 ml of a 1 N n-butyllithium solution (in hexane) are added dropwise at -75°C to a mixture of 12.1 g of 4-methoxy-3-(3-methoxypropyloxy)-bromobenzene and 9.7 ml of 4-  
15 methylmorpholine in 75 ml of tetrahydrofuran. The reaction mixture is stirred for a further 20 minutes at -75°C and then, at from -75°C to -60°C, a suspension of magnesium bromide in tetrahydrofuran (freshly prepared from 1.6 g of magnesium powder and 5.7 ml of 1,2-dibromoethane in 150 ml of tetrahydrofuran) is  
20 added. The reaction mixture is stirred for a further 30 minutes and then, at -75°C, a solution of 8.84 g of 3(S)-isopropyl-5(S)-[1(S)-azido-3(S)-isopropyl-4-oxobutyl]-tetrahydrofuran-2-one in 75 ml of tetrahydrofuran is added. The reaction mixture is then stirred for 15 minutes at -75°C and subsequently 70 ml of  
25 saturated ammonium chloride solution are added. The reaction mixture is then poured into 180 ml of saturated sodium chloride solution:water (1:1) and extracted with ethyl acetate (2x360 ml). The organic phases are dried over magnesium sulfate and concentrated by evaporation. The title compound is obtained by  
30 purifying the residue by FC (240 g of silica gel, ethyl acetate/hexane=1:2):  $R_f$  (ethyl acetate/hexane=1:2)=0.16; HPLC  $R_t$  =18.53 and 19.49 minutes (diastereoisomeric mixture).



## d) 4-Methoxy-3-(3-methoxypropyloxy)-bromobenzene

66.0 g of potassium carbonate and 3-methoxy-1-bromopropane are added at room temperature to a solution of 64.6 g of 5-bromo-2-methoxyphenol in 350 ml of acetonitrile. The reaction mixture is stirred under reflux for 14 hours. After removal of the solvent by evaporation, 1200 ml of ice/water are added to the residue and extraction is carried out with ether. The organic extracts are washed with saturated sodium chloride solution, dried over magnesium sulfate and concentrated by evaporation. Distillation under a high vacuum yields the title compound: R<sub>sub.e</sub> (hexane/ethyl acetate=4:1)=0.33; b.p.=126°-129°C./1.4 mbar; HPLC R<sub>t</sub> =16.38 minutes; MS (M<sup>+</sup>)=274, 276.

**EXAMPLE 186**

5(S)-Amino-4(S),8(R or S)-dihydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)-amide hydrochloride

The title compound is obtained analogously to Example 185 starting from 5(S)-azido-4(S),8(R or S)-dihydroxy-2(S),7(S)-diisopropyl-8-[4-methoxy-3-(3-methoxypropyloxy)-phenyl]-octanoic acid N-(2-carbamoyl-2,2-dimethyl-ethyl)-amide: HPLC R<sub>t</sub> =10.68; FAB-MS (M+H)<sup>+</sup> =568.

The starting material is prepared analogously to Example 185a) from 3(S)-isopropyl-5(S)-{1(S)-azido-4(R or S)-hydroxy-3(S)-isopropyl-4-[4-methoxy-3-(3-methoxy-propyloxy)-phenyl]-butyl}-tetrahydrofuran-2-one (Example 185 b) diastereoisomer A).

The methods of the invention employ therapeutically effective amounts: for oral administration from about 0.1 mg/day to about 1,000 mg/day; for parenteral, sublingual, intranasal, intrathecal administration from about 0.5 to about

100 mg/day; for depo administration and implants from about 0.5 mg/day to about 50 mg/day; for topical administration from about 0.5 mg/day to about 200 mg/day; for rectal administration from about 0.5 mg to about 500 mg.

5        In a preferred aspect, the therapeutically effective amounts for oral administration is from about 1 mg/day to about 100 mg/day; and for parenteral administration from about 5 to about 50 mg daily.

10        In a more preferred aspect, the therapeutically effective amounts for oral administration is from about 5 mg/day to about 50 mg/day.

15        The compounds, compositions, and methods of the invention are useful for treating humans who have Alzheimer's Disease (AD), for helping prevent or delay the onset of AD, for treating subjects with mild cognitive impairment (MCI), and preventing or delaying the onset of AD in those subjects who would otherwise be expected to progress from MCI to AD, for treating Down's syndrome, for treating Hereditary Cerebral Hemorrhage with  
20        Amyloidosis of the Dutch Type, for treating cerebral beta-amyloid angiopathy and preventing its potential consequences such as single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, for treating dementia  
25        associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, and diffuse Lewy body type AD.

30        The compounds of the invention possess beta-secretase inhibitory activity. The inhibitory activities of the compounds of the invention are readily demonstrated, for example, using one or more of the assays described herein or known in the art.

The compounds of formula 1 can form salts when reacted with acids. Pharmaceutically acceptable salts are preferred over the corresponding amines of formula 1 since they frequently produce compounds which are generally more water soluble, stable and/or more crystalline. Pharmaceutically acceptable salts are any salt which retains the activity of the parent compound and does not impart any deleterious or undesirable effect on the subject to whom it is administered and in the context in which it is administered. Pharmaceutically acceptable salts include acid addition salts of both inorganic and organic acids. The preferred pharmaceutically acceptable salts include salts of the following acids acetic, aspartic, benzenesulfonic, benzoic, bicarbonic, bisulfuric, bitartaric, butyric, calcium edetate, camsylic, carbonic, chlorobenzoic, citric, edetic, edisylic, estolic, esyl, esylic, formic, fumaric, gluceptic, gluconic, glutamic, glycollylarsanilic, hexamic, hexylresorcinoic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxynaphthoic, isethionic, lactic, lactobionic, maleic, malic, malonic, mandelic, methanesulfonic, methylnitric, methylsulfuric, mucic, muconic, napsylic, nitric, oxalic, p-nitromethanesulfonic, pamoic, pantothenic, phosphoric, monohydrogen phosphoric, dihydrogen phosphoric, phthalic, polygalactouronic, propionic, salicylic, stearic, succinic, succinic, sulfamic, sulfanilic, sulfonic, sulfuric, tannic, tartaric, teoclic and toluenesulfonic. For other acceptable salts, see *Int. J. Pharm.*, 33, 201-217 (1986) and *J. Pharm. Sci.*, 66(1), 1, (1977).

The present invention provides kits, and methods for inhibiting beta-secretase enzyme activity and A beta peptide production. Inhibition of beta-secretase enzyme activity halts or reduces the production of A beta from APP and reduces or eliminates the formation of beta-amyloid deposits in the brain.

**Methods of the Invention**

The compounds of the invention, and pharmaceutically acceptable salts thereof, are useful for treating humans or animals suffering from a condition characterized by a pathological form of beta-amyloid peptide, such as beta-amyloid plaques, and for helping to prevent or delay the onset of such a condition. For example, the compounds are useful for treating Alzheimer's disease, for helping prevent or delay the onset of Alzheimer's disease, for treating subjects with MCI (mild cognitive impairment) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobal hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, and diffuse Lewy body type Alzheimer's disease. The compounds and compositions of the invention are particularly useful for treating, preventing, or slowing the progression of Alzheimer's disease. When treating or preventing these diseases, the compounds of the invention can either be used individually or in combination, as is best for the subject.

With regard to these diseases, the term "treating" means that compounds of the invention can be used in humans with existing disease. The compounds of the invention will not necessarily cure the subject who has the disease but will delay or slow the progression or prevent further progression of the disease thereby giving the individual a more useful life span.

The term "preventing" means that that if the compounds of the invention are administered to those who do not now have the disease but who would normally develop the disease or be at increased risk for the disease, they will not develop the disease. In addition, "preventing" also includes delaying the development of the disease in an individual who will ultimately develop the disease or would be at risk for the disease due to age, familial history, genetic or chromosomal abnormalities, and/or due to the presence of one or more biological markers for the disease, such as a known genetic mutation of APP or APP cleavage products in brain tissues or fluids. By delaying the onset of the disease, compounds of the invention have prevented the individual from getting the disease during the period in which the individual would normally have gotten the disease or reduce the rate of development of the disease or some of its effects but for the administration of compounds of the invention up to the time the individual ultimately gets the disease. Preventing also includes administration of the compounds of the invention to those individuals thought to be predisposed to the disease.

In a preferred aspect, the compounds of the invention are useful for slowing the progression of disease symptoms.

In another preferred aspect, the compounds of the invention are useful for preventing the further progression of disease symptoms.

In treating or preventing the above diseases, the compounds of the invention are administered in a therapeutically effective amount. The therapeutically effective amount will vary depending on the particular compound used and the route of administration, as is known to those skilled in the art.

In treating a subject displaying any of the diagnosed above conditions a physician may administer a compound of the invention immediately and continue administration indefinitely,

as needed. In treating subjects who are not diagnosed as having Alzheimer's disease, but who are believed to be at substantial risk for Alzheimer's disease, the physician should preferably start treatment when the subject first experiences early pre-  
5 Alzheimer's symptoms such as, memory or cognitive problems associated with aging. In addition, there are some subjects who may be determined to be at risk for developing Alzheimer's through the detection of a genetic marker such as APOE4 or other biological indicators that are predictive for Alzheimer's  
10 disease. In these situations, even though the subject does not have symptoms of the disease, administration of the compounds of the invention may be started before symptoms appear, and treatment may be continued indefinitely to prevent or delay the onset of the disease.

#### Dosage Forms and Amounts

The compounds of the invention can be administered orally, parenterally, (IV, IM, depo-IM, SQ, and depo SQ), sublingually, intranasally (inhalation), intrathecally, topically, or  
20 rectally. Dosage forms known to those of skill in the art are suitable for delivery of the compounds of the invention.

Compositions are provided that contain therapeutically effective amounts of the compounds of the invention. The compounds are preferably formulated into suitable pharmaceutical  
25 preparations such as tablets, capsules, or elixirs for oral administration or in sterile solutions or suspensions for parenteral administration. Typically the compounds described above are formulated into pharmaceutical compositions using techniques and procedures well known in the art.

30 About 1 to 500 mg of a compound or mixture of compounds of the invention or a physiologically acceptable salt or ester is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a

unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in those compositions or preparations is such that a suitable dosage in the range indicated is obtained. The compositions are preferably  
5 formulated in a unit dosage form, each dosage containing from about 2 to about 100 mg, more preferably about 10 to about 30 mg of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined  
10 quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

To prepare compositions, one or more compounds of the invention are mixed with a suitable pharmaceutically acceptable  
15 carrier. Upon mixing or addition of the compound(s), the resulting mixture may be a solution, suspension, emulsion, or the like. Liposomal suspensions may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. The  
20 form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for lessening or ameliorating at least one symptom of the disease, disorder, or  
25 condition treated and may be empirically determined.

Pharmaceutical carriers or vehicles suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration. In addition, the active  
30 materials can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, or have another action. The compounds may be formulated as the sole pharmaceutically active ingredient in

the composition or may be combined with other active ingredients.

Where the compounds exhibit insufficient solubility, methods for solubilizing may be used. Such methods are known and include, but are not limited to, using cosolvents such as dimethylsulfoxide (DMSO), using surfactants such as Tween®, and dissolution in aqueous sodium bicarbonate. Derivatives of the compounds, such as salts or prodrugs may also be used in formulating effective pharmaceutical compositions.

The concentration of the compound is effective for delivery of an amount upon administration that lessens or ameliorates at least one symptom of the disorder for which the compound is administered. Typically, the compositions are formulated for single dosage administration.

The compounds of the invention may be prepared with carriers that protect them against rapid elimination from the body, such as time-release formulations or coatings. Such carriers include controlled release formulations, such as, but not limited to, microencapsulated delivery systems. The active compound is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the subject treated. The therapeutically effective concentration may be determined empirically by testing the compounds in known *in vitro* and *in vivo* model systems for the treated disorder.

The compounds and compositions of the invention can be enclosed in multiple or single dose containers. The enclosed compounds and compositions can be provided in kits, for example, including component parts that can be assembled for use. For example, a compound inhibitor in lyophilized form and a suitable diluent may be provided as separated components for combination prior to use. A kit may include a compound inhibitor and a second therapeutic agent for co-administration. The inhibitor



and second therapeutic agent may be provided as separate component parts. A kit may include a plurality of containers, each container holding one or more unit dose of the compound of the invention. The containers are preferably adapted for the  
5 desired mode of administration, including, but not limited to tablets, gel capsules, sustained-release capsules, and the like for oral administration; depot products, pre-filled syringes, ampoules, vials, and the like for parenteral administration; and  
10 patches, medipads, creams, and the like for topical administration.

The concentration of active compound in the drug composition will depend on absorption, inactivation, and excretion rates of the active compound, the dosage schedule, and amount administered as well as other factors known to those of  
15 skill in the art.

The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the disease being treated  
20 and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific  
25 dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or  
30 practice of the claimed compositions.

If oral administration is desired, the compound should be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be

formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

5        Oral compositions will generally include an inert diluent or an edible carrier and may be compressed into tablets or enclosed in gelatin capsules. For the purpose of oral therapeutic administration, the active compound or compounds can be incorporated with excipients and used in the form of tablets,  
10 capsules, or troches. Pharmaceutically compatible binding agents and adjuvant materials can be included as part of the composition.

      The tablets, pills, capsules, troches, and the like can contain any of the following ingredients or compounds of a  
15 similar nature: a binder such as, but not limited to, gum tragacanth, acacia, corn starch, or gelatin; an excipient such as microcrystalline cellulose, starch, or lactose; a disintegrating agent such as, but not limited to, alginic acid and corn starch; a lubricant such as, but not limited to,  
20 magnesium stearate; a gildant, such as, but not limited to, colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; and a flavoring agent such as peppermint, methyl salicylate, or fruit flavoring.

      When the dosage unit form is a capsule, it can contain, in  
25 addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials, which modify the physical form of the dosage unit, for example, coatings of sugar and other enteric agents. The compounds can also be administered as a component of an  
30 elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings, and flavors.

The active materials can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action.

Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include any of the following components: a sterile diluent such as water for injection, saline solution, fixed oil, a naturally occurring vegetable oil such as sesame oil, coconut oil, peanut oil, cottonseed oil, and the like, or a synthetic fatty vehicle such as ethyl oleate, and the like, polyethylene glycol, glycerine, propylene glycol, or other synthetic solvent; antimicrobial agents such as benzyl alcohol and methyl parabens; antioxidants such as ascorbic acid and sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates, and phosphates; and agents for the adjustment of tonicity such as sodium chloride and dextrose. Parenteral preparations can be enclosed in ampoules, disposable syringes, or multiple dose vials made of glass, plastic, or other suitable material. Buffers, preservatives, antioxidants, and the like can be incorporated as required.

Where administered intravenously, suitable carriers include physiological saline, phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents such as glucose, polyethylene glycol, polypropyleneglycol, and mixtures thereof. Liposomal suspensions including tissue-targeted liposomes may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known for example, as described in U.S. Patent No. 4,522,811.

The active compounds may be prepared with carriers that protect the compound against rapid elimination from the body, such as time-release formulations or coatings. Such carriers include controlled release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and

biodegradable, biocompatible polymers such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid, and the like. Methods for preparation of such formulations are known to those skilled in the art.

The compounds of the invention can be administered orally, parenterally (IV, IM, depo-IM, SQ, and depo-SQ), sublingually, intranasally (inhalation), intrathecally, topically, or rectally. Dosage forms known to those skilled in the art are suitable for delivery of the compounds of the invention.

Compounds of the invention may be administered enterally or parenterally. When administered orally, compounds of the invention can be administered in usual dosage forms for oral administration as is well known to those skilled in the art. These dosage forms include the usual solid unit dosage forms of tablets and capsules as well as liquid dosage forms such as solutions, suspensions, and elixirs. When the solid dosage forms are used, it is preferred that they be of the sustained release type so that the compounds of the invention need to be administered only once or twice daily.

The oral dosage forms are administered to the subject 1, 2, 3, or 4 times daily. It is preferred that the compounds of the invention be administered either three or fewer times, more preferably once or twice daily. Hence, it is preferred that the compounds of the invention be administered in oral dosage form. It is preferred that whatever oral dosage form is used, that it be designed so as to protect the compounds of the invention from the acidic environment of the stomach. Enteric coated tablets are well known to those skilled in the art. In addition, capsules filled with small spheres each coated to protect from the acidic stomach, are also well known to those skilled in the art.

When administered orally, an administered amount therapeutically effective to inhibit beta-secretase activity, to inhibit A beta production, to inhibit A beta deposition, or to treat or prevent AD is from about 0.1 mg/day to about 1,000 mg/day. It is preferred that the oral dosage is from about 1 mg/day to about 100 mg/day. It is more preferred that the oral dosage is from about 5 mg/day to about 50 mg/day. It is understood that while a subject may be started at one dose, that dose may be varied over time as the subject's condition changes.

Compounds of the invention may also be advantageously delivered in a nano crystal dispersion formulation. Preparation of such formulations is described, for example, in U.S. Patent 5,145,684. Nano crystalline dispersions of HIV protease inhibitors and their method of use are described in U.S. Patent No. 6,045,829. The nano crystalline formulations typically afford greater bioavailability of drug compounds.

The compounds of the invention can be administered parenterally, for example, by IV, IM, depo-IM, SC, or depo-SC. When administered parenterally, a therapeutically effective amount of about 0.5 to about 100 mg/day, preferably from about 5 to about 50 mg daily should be delivered. When a depot formulation is used for injection once a month or once every two weeks, the dose should be about 0.5 mg/day to about 50 mg/day, or a monthly dose of from about 15 mg to about 1,500 mg. In part because of the forgetfulness of the subjects with Alzheimer's disease, it is preferred that the parenteral dosage form be a depo formulation.

The compounds of the invention can be administered sublingually. When given sublingually, the compounds of the invention should be given one to four times daily in the amounts described above for IM administration.

The compounds of the invention can be administered intranasally. When given by this route, the appropriate dosage

forms are a nasal spray or dry powder, as is known to those skilled in the art. The dosage of the compounds of the invention for intranasal administration is the amount described above for IM administration.

5       The compounds of the invention can be administered intrathecally. When given by this route the appropriate dosage form can be a parenteral dosage form as is known to those skilled in the art. The dosage of the compounds of the invention for intrathecal administration is the amount described  
10   above for IM administration.

      The compounds of the invention can be administered topically. When given by this route, the appropriate dosage form is a cream, ointment, or patch. Because of the amount of the compounds of the invention to be administered, the patch is  
15   preferred. When administered topically, the dosage is from about 0.5 mg/day to about 200 mg/day. Because the amount that can be delivered by a patch is limited, two or more patches may be used. The number and size of the patch is not important, what is important is that a therapeutically effective amount of  
20   the compounds of the invention be delivered as is known to those skilled in the art. The compounds of the invention can be administered rectally by suppository as is known to those skilled in the art. When administered by suppository, the therapeutically effective amount is from about 0.5 mg to about  
25   500 mg.

      The compounds of the invention can be administered by implants as is known to those skilled in the art. When administering a compound of the invention by implant, the therapeutically effective amount is the amount described above  
30   for depot administration.

      The invention here is the new compounds of the invention and new methods of using the compounds of the invention. Given a particular compound of the invention and a desired dosage

form, one skilled in the art would know how to prepare and administer the appropriate dosage form.

The compounds of the invention are used in the same manner, by the same routes of administration, using the same pharmaceutical dosage forms, and at the same dosing schedule as described above, for preventing disease or treating subjects with MCI (mild cognitive impairment) and preventing or delaying the onset of Alzheimer's disease in those who would progress from MCI to AD, for treating or preventing Down's syndrome, for treating humans who have Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-Type, for treating cerebral amyloid angiopathy and preventing its potential consequences, i.e. single and recurrent lobar hemorrhages, for treating other degenerative dementias, including dementias of mixed vascular and degenerative origin, dementia associated with Parkinson's disease, dementia associated with progressive supranuclear palsy, dementia associated with cortical basal degeneration, and diffuse Lewy body type of Alzheimer's disease.

The compounds of the invention can be used with each other or with other agents used to treat or prevent the conditions listed above. Such agents include gamma-secretase inhibitors, anti-amyloid vaccines and pharmaceutical agents such as donepezil hydrochloride (ARICEPT® Tablets), tacrine hydrochloride (COGNEX® Capsules) or other acetylcholine esterase inhibitors and with direct or indirect neurotropic agents of the future.

In addition, the compounds of the invention can also be used with inhibitors of P-glycoprotein (P-gp). The use of P-gp inhibitors is known to those skilled in the art. See for example, *Cancer Research*, 53, 4595-4602 (1993), *Clin. Cancer Res.*, 2, 7-12 (1996), *Cancer Research*, 56, 4171-4179 (1996), International Publications WO99/64001 and WO01/10387. The important thing is that the blood level of the P-gp inhibitor be

such that it exerts its effect in inhibiting P-gp from decreasing brain blood levels of the compounds of the invention. To that end the P-gp inhibitor and the compounds of the invention can be administered at the same time, by the same or  
5 different route of administration, or at different times. The important thing is not the time of administration but having an effective blood level of the P-gp inhibitor.

Suitable P-gp inhibitors include cyclosporin A, verapamil, tamoxifen, quinidine, Vitamin E-TGPS, ritonavir, megestrol  
10 acetate, progesterone, rapamycin, 10,11-methanodibenzosuberane, phenothiazines, acridine derivatives such as GF120918, FK506, VX-710, LY335979, PSC-833, GF-102,918 and other steroids. It is to be understood that additional agents will be found that do the same function and are also considered to be useful.

15 The P-gp inhibitors can be administered orally, parenterally, (IV, IM, IM-depo, SQ, SQ-depo), topically, sublingually, rectally, intranasally, intrathecally and by implant.

The therapeutically effective amount of the P-gp inhibitors  
20 is from about 0.1 to about 300 mg/kg/day, preferably about 0.1 to about 150 mg/kg daily. It is understood that while a subject may be started on one dose, that dose may have to be varied over time as the subject's condition changes.

When administered orally, the P-gp inhibitors can be  
25 administered in usual dosage forms for oral administration as is known to those skilled in the art. These dosage forms include the usual solid unit dosage forms of tablets and capsules as well as liquid dosage forms such as solutions, suspensions and elixirs. When the solid dosage forms are used, it is preferred  
30 that they be of the sustained release type so that the P-gp inhibitors need to be administered only once or twice daily. The oral dosage forms are administered to the subject one thru four times daily. It is preferred that the P-gp inhibitors be



administered either three or fewer times a day, more preferably once or twice daily. Hence, it is preferred that the P-gp inhibitors be administered in solid dosage form and further it is preferred that the solid dosage form be a sustained release  
5 form which permits once or twice daily dosing. It is preferred that what ever dosage form is used, that it be designed so as to protect the P-gp inhibitors from the acidic environment of the stomach. Enteric coated tablets are well known to those skilled in the art. In addition, capsules filled with small spheres  
10 each coated to protect from the acidic stomach, are also well known to those skilled in the art.

In addition, the P-gp inhibitors can be administered parenterally. When administered parenterally they can be administered IV, IM, depo-IM, SQ or depo-SQ. The P-gp  
15 inhibitors can be given sublingually. When given sublingually, the P-gp inhibitors should be given one thru four times daily in the same amount as for IM administration.

The P-gp inhibitors can be given intranasally. When given by this route of administration, the appropriate dosage forms  
20 are a nasal spray or dry powder as is known to those skilled in the art. The dosage of the P-gp inhibitors for intranasal administration is the same as for IM administration.

The P-gp inhibitors can be given intrathecally. When given by this route of administration the appropriate dosage form can  
25 be a parenteral dosage form as is known to those skilled in the art.

The P-gp inhibitors can be given topically. When given by this route of administration, the appropriate dosage form is a cream, ointment or patch. Because of the amount of the P-gp  
30 inhibitors needed to be administered the path is preferred. However, the amount that can be delivered by a patch is limited. Therefore, two or more patches may be required. The number and size of the patch is not important, what is important is that a

therapeutically effective amount of the P-gp inhibitors be delivered as is known to those skilled in the art. The P-gp inhibitors can be administered rectally by suppository as is known to those skilled in the art.

5 The P-gp inhibitors can be administered by implants as is known to those skilled in the art.

There is nothing novel about the route of administration or the dosage forms for administering the P-gp inhibitors. Given a particular P-gp inhibitor, and a desired dosage form, one  
10 skilled in the art would know how to prepare the appropriate dosage form for the P-gp inhibitor.

The compounds employed in the methods of the invention can be used in combination, with each other or with other therapeutic agents or approaches used to treat or prevent the  
15 conditions listed above. Such agents or approaches include: acetylcholine esterase inhibitors such as tacrine (tetrahydroaminoacridine, marketed as COGNEX®), donepezil hydrochloride, (marketed as Aricept® and rivastigmine (marketed as Exelon®); gamma-secretase inhibitors; anti-inflammatory  
20 agents such as cyclooxygenase II inhibitors; anti-oxidants such as Vitamin E and ginkgolides; immunological approaches, such as, for example, immunization with A beta peptide or administration of anti-A beta peptide antibodies; statins; and direct or indirect neurotropic agents such as Cerebrolysin®, AIT-082  
25 (Emilieu, 2000, Arch. Neurol. 57:454), and other neurotropic agents of the future.

It should be apparent to one skilled in the art that the exact dosage and frequency of administration will depend on the particular compounds employed in the methods of the invention  
30 administered, the particular condition being treated, the severity of the condition being treated, the age, weight, general physical condition of the particular subject, and other

medication the individual may be taking as is well known to administering physicians who are skilled in this art.

#### Inhibition of APP Cleavage

5       The compounds of the invention inhibit cleavage of APP between Met595 and Asp596 numbered for the APP695 isoform, or a mutant thereof, or at a corresponding site of a different isoform, such as APP751 or APP770, or a mutant thereof (sometimes referred to as the "beta secretase site"). While not  
10       wishing to be bound by a particular theory, inhibition of beta-secretase activity is thought to inhibit production of beta amyloid peptide (A beta). Inhibitory activity is demonstrated in one of a variety of inhibition assays, whereby cleavage of an APP substrate in the presence of a beta-secretase enzyme is  
15       analyzed in the presence of the inhibitory compound, under conditions normally sufficient to result in cleavage at the beta-secretase cleavage site. Reduction of APP cleavage at the beta-secretase cleavage site compared with an untreated or inactive control is correlated with inhibitory activity. Assay  
20       systems that can be used to demonstrate efficacy of the compound inhibitors of the invention are known. Representative assay systems are described, for example, in U.S. Patents No. 5,942,400, 5,744,346, as well as in the Examples below.

      The enzymatic activity of beta-secretase and the production  
25       of A beta can be analyzed *in vitro* or *in vivo*, using natural, mutated, and/or synthetic APP substrates, natural, mutated, and/or synthetic enzyme, and the test compound. The analysis may involve primary or secondary cells expressing native, mutant, and/or synthetic APP and enzyme, animal models  
30       expressing native APP and enzyme, or may utilize transgenic animal models expressing the substrate and enzyme. Detection of enzymatic activity can be by analysis of one or more of the cleavage products, for example, by immunoassay, fluorometric or

chromogenic assay, HPLC, or other means of detection. Inhibitory compounds are determined as those having the ability to decrease the amount of beta-secretase cleavage product produced in comparison to a control, where beta-secretase  
5 mediated cleavage in the reaction system is observed and measured in the absence of inhibitory compounds.

#### **Beta-Secretase**

Various forms of beta-secretase enzyme are known, and are  
10 available and useful for assay of enzyme activity and inhibition of enzyme activity. These include native, recombinant, and synthetic forms of the enzyme. Human beta-secretase is known as Beta Site APP Cleaving Enzyme (BACE), Asp2, and memapsin 2, and has been characterized, for example, in U.S. Patent No.  
15 5,744,346 and published PCT patent applications WO98/22597, WO00/03819, WO01/23533, and WO00/17369, as well as in literature publications (Hussain et al., 1999, *Mol. Cell. Neurosci.* 14:419-427; Vassar et al., 1999, *Science* 286:735-741; Yan et al., 1999, *Nature* 402:533-537; Sinha et al., 1999, *Nature*  
20 40:537-540; and Lin et al., 2000, *PNAS USA* 97:1456-1460). Synthetic forms of the enzyme have also been described (WO98/22597 and WO00/17369). Beta-secretase can be extracted and purified from human brain tissue and can be produced in cells, for example mammalian cells expressing recombinant  
25 enzyme.

Preferred methods employ compounds that are effective to inhibit 50% of beta-secretase enzymatic activity at a concentration of less than about 50 micromolar, preferably at a concentration of less than about 10 micromolar, more preferably  
30 less than about 1 micromolar, and most preferably less than about 10 nanomolar.

**APP Substrate**

Assays that demonstrate inhibition of beta-secretase-mediated cleavage of APP can utilize any of the known forms of APP, including the 695 amino acid "normal" isotype described by Kang et al., 1987, *Nature* 325:733-6, the 770 amino acid isotype described by Kitaguchi et. al., 1981, *Nature* 331:530-532, and variants such as the Swedish Mutation (KM670-1NL) (APP-SW), the London Mutation (V7176F), and others. See, for example, U.S. Patent No. 5,766,846 and also Hardy, 1992, *Nature Genet.* 1:233-234, for a review of known variant mutations. Additional useful substrates include the dibasic amino acid modification, APP-KK disclosed, for example, in WO 00/17369, fragments of APP, and synthetic peptides containing the beta-secretase cleavage site, wild type (WT) or mutated form, e.g., SW, as described, for example, in U.S. Patent No 5,942,400 and WO00/03819.

The APP substrate contains the beta-secretase cleavage site of APP (KM-DA or NL-DA) for example, a complete APP peptide or variant, an APP fragment, a recombinant or synthetic APP, or a fusion peptide. Preferably, the fusion peptide includes the beta-secretase cleavage site fused to a peptide having a moiety useful for enzymatic assay, for example, having isolation and/or detection properties. A useful moiety may be an antigenic epitope for antibody binding, a label or other detection moiety, a binding substrate, and the like.

**Antibodies**

Products characteristic of APP cleavage can be measured by immunoassay using various antibodies, as described, for example, in Pirttila et al., 1999, *Neuro. Lett.* 249:21-4, and in U.S. Patent No. 5,612,486. Useful antibodies to detect A beta include, for example, the monoclonal antibody 6E10 (Senetek, St. Louis, MO) that specifically recognizes an epitope on amino

acids 1-16 of the A beta peptide; antibodies 162 and 164 (New York State Institute for Basic Research, Staten Island, NY) that are specific for human A beta 1-40 and 1-42, respectively; and antibodies that recognize the junction region of beta-amyloid peptide, the site between residues 16 and 17, as described in U.S. Patent No. 5,593,846. Antibodies raised against a synthetic peptide of residues 591 to 596 of APP and SW192 antibody raised against 590-596 of the Swedish mutation are also useful in immunoassay of APP and its cleavage products, as described in U.S. Patent Nos. 5,604,102 and 5,721,130.

#### **Assay Systems**

Assays for determining APP cleavage at the beta-secretase cleavage site are well known in the art. Exemplary assays, are described, for example, in U.S. Patent Nos. 5,744,346 and 5,942,400, and described in the Examples below.

#### **Cell Free Assays**

Exemplary assays that can be used to demonstrate the inhibitory activity of the compounds of the invention are described, for example, in WO00/17369, WO 00/03819, and U.S. Patents No. 5,942,400 and 5,744,346. Such assays can be performed in cell-free incubations or in cellular incubations using cells expressing a beta-secretase and an APP substrate having a beta-secretase cleavage site.

An APP substrate containing the beta-secretase cleavage site of APP, for example, a complete APP or variant, an APP fragment, or a recombinant or synthetic APP substrate containing the amino acid sequence: KM-DA or NL-DA, is incubated in the presence of beta-secretase enzyme, a fragment thereof, or a synthetic or recombinant polypeptide variant having beta-secretase activity and effective to cleave the beta-secretase cleavage site of APP, under incubation conditions suitable for

the cleavage activity of the enzyme. Suitable substrates optionally include derivatives that may be fusion proteins or peptides that contain the substrate peptide and a modification useful to facilitate the purification or detection of the peptide or its beta-secretase cleavage products. Useful modifications include the insertion of a known antigenic epitope for antibody binding; the linking of a label or detectable moiety, the linking of a binding substrate, and the like.

Suitable incubation conditions for a cell-free *in vitro* assay include, for example: approximately 200 nanomolar to 10 micromolar substrate, approximately 10 to 200 picomolar enzyme, and approximately 0.1 nanomolar to 10 micromolar inhibitor compound, in aqueous solution, at an approximate pH of 4-7, at approximately 37°C, for a time period of approximately 10 minutes to 3 hours. These incubation conditions are exemplary only, and can be varied as required for the particular assay components and/or desired measurement system. Optimization of the incubation conditions for the particular assay components should account for the specific beta-secretase enzyme used and its pH optimum, any additional enzymes and/or markers that might be used in the assay, and the like. Such optimization is routine and will not require undue experimentation.

One useful assay utilizes a fusion peptide having maltose binding protein (MBP) fused to the C-terminal 125 amino acids of APP-SW. The MBP portion is captured on an assay substrate by anti-MBP capture antibody. Incubation of the captured fusion protein in the presence of beta-secretase results in cleavage of the substrate at the beta-secretase cleavage site. Analysis of the cleavage activity can be, for example, by immunoassay of cleavage products. One such immunoassay detects a unique epitope exposed at the carboxy terminus of the cleaved fusion protein, for example, using the antibody SW192. This assay is described, for example, in U.S. Patent No 5,942,400.

### Cellular Assay

Numerous cell-based assays can be used to analyze beta-secretase activity and/or processing of APP to release A beta.

5 Contact of an APP substrate with a beta-secretase enzyme within the cell and in the presence or absence of a compound inhibitor of the invention can be used to demonstrate beta-secretase inhibitory activity of the compound. Preferably, assay in the presence of a useful inhibitory compound provides at least about  
10 30%, most preferably at least about 50% inhibition of the enzymatic activity, as compared with a non-inhibited control.

In one embodiment, cells that naturally express beta-secretase are used. Alternatively, cells are modified to express a recombinant beta-secretase or synthetic variant enzyme  
15 as discussed above. The APP substrate may be added to the culture medium and is preferably expressed in the cells. Cells that naturally express APP, variant or mutant forms of APP, or cells transformed to express an isoform of APP, mutant or variant APP, recombinant or synthetic APP, APP fragment, or  
20 synthetic APP peptide or fusion protein containing the beta-secretase APP cleavage site can be used, provided that the expressed APP is permitted to contact the enzyme and enzymatic cleavage activity can be analyzed.

Human cell lines that normally process A beta from APP  
25 provide a useful means to assay inhibitory activities of the compounds of the invention. Production and release of A beta and/or other cleavage products into the culture medium can be measured, for example by immunoassay, such as Western blot or enzyme-linked immunoassay (EIA) such as by ELISA.

30 Cells expressing an APP substrate and an active beta-secretase can be incubated in the presence of a compound inhibitor to demonstrate inhibition of enzymatic activity as compared with a control. Activity of beta-secretase can be



measured by analysis of one or more cleavage products of the APP substrate. For example, inhibition of beta-secretase activity against the substrate APP would be expected to decrease release of specific beta-secretase induced APP cleavage products such as

5 A beta.

Although both neural and non-neural cells process and release A beta, levels of endogenous beta-secretase activity are low and often difficult to detect by EIA. The use of cell types known to have enhanced beta-secretase activity, enhanced  
10 processing of APP to A beta, and/or enhanced production of A beta are therefore preferred. For example, transfection of cells with the Swedish Mutant form of APP (APP-SW); with APP-KK; or with APP-SW-KK provides cells having enhanced beta-secretase activity and producing amounts of A beta that can be readily  
15 measured.

In such assays, for example, the cells expressing APP and beta-secretase are incubated in a culture medium under conditions suitable for beta-secretase enzymatic activity at its cleavage site on the APP substrate. On exposure of the cells to  
20 the compound inhibitor, the amount of A beta released into the medium and/or the amount of CTF99 fragments of APP in the cell lysates is reduced as compared with the control. The cleavage products of APP can be analyzed, for example, by immune reactions with specific antibodies, as discussed above.

25 Preferred cells for analysis of beta-secretase activity include primary human neuronal cells, primary transgenic animal neuronal cells where the transgene is APP, and other cells such as those of a stable 293 cell line expressing APP, for example, APP-SW.

30

#### **In vivo Assays: Animal Models**

Various animal models can be used to analyze beta-secretase activity and /or processing of APP to release A beta, as

described above. For example, transgenic animals expressing APP substrate and beta-secretase enzyme can be used to demonstrate inhibitory activity of the compounds of the invention. Certain transgenic animal models have been described, for example, in U.S. Patent Nos.: 5,877,399; 5,612,486; 5,387,742; 5,720,936; 5,850,003; 5,877,015,, and 5,811,633, and in Ganes et al., 1995, *Nature* 373:523. Preferred are animals that exhibit characteristics associated with the pathophysiology of AD. Administration of the compound inhibitors of the invention to the transgenic mice described herein provides an alternative method for demonstrating the inhibitory activity of the compounds. Administration of the compounds in a pharmaceutically effective carrier and via an administrative route that reaches the target tissue in an appropriate therapeutic amount is also preferred.

Inhibition of beta-secretase mediated cleavage of APP at the beta-secretase cleavage site and of A beta release can be analyzed in these animals by measure of cleavage fragments in the animal's body fluids such as cerebral fluid or tissues. Analysis of brain tissues for A beta deposits or plaques is preferred.

On contacting an APP substrate with a beta-secretase enzyme in the presence of an inhibitory compound of the invention and under conditions sufficient to permit enzymatic mediated cleavage of APP and/or release of A beta from the substrate, the compounds of the invention are effective to reduce beta-secretase-mediated cleavage of APP at the beta-secretase cleavage site and/or effective to reduce released amounts of A beta. Where such contacting is the administration of the inhibitory compounds of the invention to an animal model, for example, as described above, the compounds are effective to reduce A beta deposition in brain tissues of the animal, and to reduce the number and/or size of beta amyloid plaques. Where

such administration is to a human subject, the compounds are effective to inhibit or slow the progression of disease characterized by enhanced amounts of A beta, to slow the progression of AD in the, and/or to prevent onset or development of AD in a subject at risk for the disease.

Unless defined otherwise, all scientific and technical terms used herein have the same meaning as commonly understood by one of skill in the art to which this invention belongs. All patents and publications referred to herein are hereby incorporated by reference for all purposes.

#### Definitions

Salts of compounds of formula 1 are preferably acid addition salts, salts with bases or, where several salt-forming groups are present, can also be mixed salts or internal salts. Salts are especially the pharmaceutically acceptable, non-toxic salts of compounds of formula 1.

In the groups of compounds of formula 1 mentioned below, it may be advantageous, for example in order to replace rather general definitions with more specific definitions, to use definitions of radicals from the above-mentioned general definitions or to insert or omit definitions from the other groups.

#### Synthesis of Compounds

The compounds of formula 1 and salts of such compounds may be prepared using the methods described in U.S. Patent No. 5,559,111 which is hereby incorporated by reference, in its entirety for all purposes.

All the process steps can be carried out under reaction conditions known per se, in the absence or, customarily, the presence of solvents or diluents, preferably those that are inert towards the reagents used and are solvents therefor, in

the absence or presence of catalysts, condensation agents or neutralising agents, for example ion exchangers, such as cation exchangers, for example in the  $H^+$  form, and, depending on the nature of the reaction and/or of the reactants, at reduced, 5 normal or elevated temperature, for example in a temperature range from approximately  $-100^{\circ}C$  to approximately  $190^{\circ}C$ , preferably from approximately  $-80^{\circ}C$  to approximately  $150^{\circ}C$ , for example from  $-80^{\circ}C$  to  $-60^{\circ}C$ , at room temperature, from  $-20^{\circ}C$  to  $40^{\circ}C$  or at the reflux temperature, under atmospheric pressure or 10 in a closed vessel, if necessary under pressure, and/or in an inert atmosphere, for example under an argon or nitrogen atmosphere.

Isomeric mixtures occurring at any stage of the reaction may be separated into the individual isomers, for example 15 diastereoisomers or enantiomers, or into any desired mixtures of isomers, for example racemates or diastereoisomeric mixtures, by any method commonly known in the art.

In certain cases, for example in the case of hydrogenation, it is possible to achieve stereo-selective reactions, which, for 20 example, enable individual isomers to be obtained more easily.

The solvents from which those suitable for a particular reaction can be selected include, for example, water, esters, such as lower alkyl-lower alkanooates, for example ethyl acetate, or isopropyl acetate; ethers, such as aliphatic ethers, for 25 example diethyl ether, or cyclic ethers, for example tetrahydrofuran, liquid aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, nitriles, such as acetonitrile, halogenated hydrocarbons, such as methylene chloride, chloroform or carbon 30 tetrachloride, acid amides, such as dimethylformamide (DMF), bases, such as heterocyclic nitrogen bases, for example pyridine, carboxylic acid anhydrides, such as lower alkanooic acid anhydrides, for example acetic anhydride, cyclic, linear or

branched hydrocarbons, such as cyclohexane, hexane or isopentane, or mixtures of those solvents, for example aqueous solutions, unless the description of the process indicates otherwise. Such solvent mixtures can also be used in the  
5 working-up, for example by chromatography or partitioning.

The compounds, including their salts, can also be obtained in the form of hydrates, or their crystals may, for example, include the solvent used for crystallization.

The invention relates also to those forms of the process in  
10 which a compound obtainable as intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example in protected form or in the form of a  
15 salt, or a compound obtainable by the process according to the invention is produced under the process conditions and further processed in situ. In the process of the present invention it is preferable to use those starting materials that lead to the compounds (of formula 1 or Ib) described in the introduction as  
20 being especially valuable. Special preference is given to reaction conditions analogous to those mentioned in the Examples.

Where necessary, protected starting compounds can be used at any stage of the process and the protecting groups removed at  
25 suitable stages of the reaction.

APP, amyloid precursor protein, is defined as any APP polypeptide, including APP variants, mutations, and isoforms, for example, as disclosed in U.S. Patent No. 5,766,846.

30 A beta, amyloid beta peptide, is defined as any peptide resulting from beta-secretase mediated cleavage of APP, including peptides of 39, 40, 41, 42, and 43 amino acids, and

extending from the beta-secretase cleavage site to amino acids 39, 40, 41, 42, or 43.

Beta-secretase (BACE1, Asp2, Memapsin 2) is an aspartyl protease that mediates cleavage of APP at the amino-terminal edge of A beta. Human beta-secretase is described, for example, in WO00/17369.

Pharmaceutically acceptable refers to those properties and/or substances that are acceptable to the subject from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, subject acceptance and bioavailability.

A therapeutically effective amount is defined as an amount effective to reduce or lessen at least one symptom of the disease being treated or to reduce or delay onset of one or more clinical markers or symptoms of the disease.

It should be noted that, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to a composition containing "a compound" includes a mixture of two or more compounds. It should also be noted that the term "or" is generally employed in its sense including "and/or" unless the content clearly dictates otherwise.

Unless defined otherwise, all scientific and technical terms used herein have the same meaning as commonly understood by one of skill in the art to which this invention belongs.

All patents and publications referred to herein are hereby incorporated by reference for all purposes.

The present invention can be better understood with reference to the following biological examples. These examples are intended to be representative of specific embodiments of the

invention, and are not intended as limiting the scope of the invention.

### BIOLOGICAL EXAMPLES

#### 5 **Example A**

##### Enzyme Inhibition Assay

The compounds of the invention are analyzed for inhibitory activity by use of the MBP-C125 assay. This assay determines the relative inhibition of beta-secretase cleavage of a model  
10 APP substrate, MBP-C125SW, by the compounds assayed as compared with an untreated control. A detailed description of the assay parameters can be found, for example, in U.S. Patent No. 5,942,400. Briefly, the substrate is a fusion peptide formed of maltose binding protein (MBP) and the carboxy terminal 125 amino  
15 acids of APP-SW, the Swedish mutation. The beta-secretase enzyme is derived from human brain tissue as described in Sinha et al, 1999, *Nature* 40:537-540) or recombinantly produced as the full-length enzyme (amino acids 1-501), and can be prepared, for example, from 293 cells expressing the recombinant cDNA, as  
20 described in WO00/47618.

Inhibition of the enzyme is analyzed, for example, by immunoassay of the enzyme's cleavage products. One exemplary ELISA uses an anti-MBP capture antibody that is deposited on precoated and blocked 96-well high binding plates, followed by  
25 incubation with diluted enzyme reaction supernatant, incubation with a specific reporter antibody, for example, biotinylated anti-SW192 reporter antibody, and further incubation with streptavidin/alkaline phosphatase. In the assay, cleavage of the intact MBP-C125SW fusion protein results in the generation  
30 of a truncated amino-terminal fragment, exposing a new SW-192 antibody-positive epitope at the carboxy terminus. Detection is effected by a fluorescent substrate signal on cleavage by the

phosphatase. ELISA only detects cleavage following Leu 596 at the substrate's APP-SW 751 mutation site.

**Specific Assay Procedure:**

5       Compounds are diluted in a 1:1 dilution series to a six-point concentration curve (two wells per concentration) in one 96-plate row per compound tested. Each of the test compounds is prepared in DMSO to make up a 10 millimolar stock solution. The stock solution is serially diluted in DMSO to obtain a final  
10       compound concentration of 200 micromolar at the high point of a 6-point dilution curve. Ten (10) microliters of each dilution is added to each of two wells on row C of a corresponding V-bottom plate to which 190 microliters of 52 millimolar NaOAc, 7.9% DMSO, pH 4.5 are pre-added. The NaOAc diluted compound  
15       plate is spun down to pellet precipitant and 20 microliters/well is transferred to a corresponding flat-bottom plate to which 30 microliters of ice-cold enzyme-substrate mixture (2.5 microliters MBP-C125SW substrate, 0.03 microliters enzyme and 24.5 microliters ice cold 0.09% TX100 per 30 microliters) is  
20       added. The final reaction mixture of 200 micromolar compound at the highest curve point is in 5% DMSO, 20 millimolar NaOAc, 0.06% TX100, at pH 4.5.

Warming the plates to 37°C starts the enzyme reaction. After 90 minutes at 37°C, 200 microliters/well cold specimen  
25       diluent is added to stop the reaction and 20 microliters/well was transferred to a corresponding anti-MBP antibody coated ELISA plate for capture, containing 80 microliters/well specimen diluent. This reaction is incubated overnight at 4°C and the ELISA is developed the next day after a 2 hour incubation with  
30       anti-192SW antibody, followed by Streptavidin-AP conjugate and fluorescent substrate. The signal is read on a fluorescent plate reader.



Relative compound inhibition potency is determined by calculating the concentration of compound that showed a fifty percent reduction in detected signal ( $IC_{50}$ ) compared to the enzyme reaction signal in the control wells with no added compound.

#### Example B

##### Cell Free Inhibition Assay Utilizing a Synthetic APP Substrate

A synthetic APP substrate that can be cleaved by beta-secretase and having N-terminal biotin and made fluorescent by the covalent attachment of Oregon green at the Cys residue is used to assay beta-secretase activity in the presence or absence of the inhibitory compounds of the invention. Useful substrates include the following:

Biotin-SEVNLDAEFRC [Oregon green] KK [SEQ ID NO: 1]  
Biotin-SEVKMDAEFRC [Oregon green] KK [SEQ ID NO: 2]  
Biotin-GLNIKTEEISEISYEVEFRC [Oregon green] KK [SEQ ID NO: 3]  
Biotin-ADRGLTTRPGSGLTNIKTEEISEVNLDAEFC [Oregon green] KK [SEQ ID NO: 4]  
Biotin-FVNQHLC<sub>ox</sub>GSHLVEALY-LVC<sub>ox</sub>GERGFFYTPKAC [Oregon green] KK [SEQ ID NO: 5]

The enzyme (0.1 nanomolar) and test compounds (0.001 - 100 micromolar) are incubated in pre-blocked, low affinity, black plates (384 well) at 37 degrees for 30 minutes. The reaction is initiated by addition of 150 millimolar substrate to a final volume of 30 microliter per well. The final assay conditions are: 0.001 - 100 micromolar compound inhibitor; 0.1 molar sodium acetate (pH 4.5); 150 nanomolar substrate; 0.1 nanomolar soluble beta-secretase; 0.001% Tween 20, and 2% DMSO. The assay mixture is incubated for 3 hours at 37 degrees C, and the reaction is terminated by the addition of a saturating concentration of immunopure streptavidin. After incubation with streptavidin at

room temperature for 15 minutes, fluorescence polarization is measured, for example, using a LJL Acquest (Ex485 nm/ Em530 nm). The activity of the beta-secretase enzyme is detected by changes in the fluorescence polarization that occur when the substrate is cleaved by the enzyme. Incubation in the presence or absence of compound inhibitor demonstrates specific inhibition of beta-secretase enzymatic cleavage of its synthetic APP substrate.

#### 10 Example C

##### Beta-Secretase Inhibition: P26-P4'SW Assay

Synthetic substrates containing the beta-secretase cleavage site of APP are used to assay beta-secretase activity, using the methods described, for example, in published PCT application WO00/47618. The P26-P4'SW substrate is a peptide of the sequence:

(biotin)CGGADRGLTTRPGSGLTNIKTEEISEVNLDAEF [SEQ ID NO: 6]

The P26-P1 standard has the sequence:

(biotin)CGGADRGLTTRPGSGLTNIKTEEISEVNL [SEQ ID NO: 7].

20 Briefly, the biotin-coupled synthetic substrates are incubated at a concentration of from about 0 to about 200 micromolar in this assay. When testing inhibitory compounds, a substrate concentration of about 1.0 micromolar is preferred. Test compounds diluted in DMSO are added to the reaction mixture, with a final DMSO concentration of 5%. Controls also contain a final DMSO concentration of 5%. The concentration of beta secretase enzyme in the reaction is varied, to give product concentrations with the linear range of the ELISA assay, about 125 to 2000 picomolar, after dilution.

30 The reaction mixture also includes 20 millimolar sodium acetate, pH 4.5, 0.06% Triton X100, and is incubated at 37 degrees C for about 1 to 3 hours. Samples are then diluted in assay buffer (for example, 145.4 nanomolar sodium chloride, 9.51

millimolar sodium phosphate, 7.7 millimolar sodium azide, 0.05% Triton X405, 6g/liter bovine serum albumin, pH 7.4) to quench the reaction, then diluted further for immunoassay of the cleavage products.

5        Cleavage products can be assayed by ELISA. Diluted samples and standards are incubated in assay plates coated with capture antibody, for example, SW192, for about 24 hours at 4 degrees C. After washing in TTBS buffer (150 millimolar sodium chloride, 25 millimolar Tris, 0.05% Tween 20, pH 7.5), the samples are  
10 incubated with streptavidin-AP according to the manufacturer's instructions. After a one hour incubation at room temperature, the samples are washed in TTBS and incubated with fluorescent substrate solution A (31.2 g/liter 2-amino-2-methyl-1-propanol, 30 mg/liter, pH 9.5). Reaction with streptavidin-alkaline  
15 phosphate permits detection by fluorescence. Compounds that are effective inhibitors of beta-secretase activity demonstrate reduced cleavage of the substrate as compared to a control.

#### Example D

#### 20    Assays using Synthetic Oligopeptide-Substrates

Synthetic oligopeptides are prepared that incorporate the known cleavage site of beta-secretase, and optionally detectable tags, such as fluorescent or chromogenic moieties. Examples of such peptides, as well as their production and detection methods  
25 are described in U.S. Patent No: 5,942,400, herein incorporated by reference. Cleavage products can be detected using high performance liquid chromatography, or fluorescent or chromogenic detection methods appropriate to the peptide to be detected, according to methods well known in the art.

30        By way of example, one such peptide has the sequence (biotin)-SEVNLDAEF [SEQ ID NO: 8], and the cleavage site is between residues 5 and 6. Another preferred substrate has the

sequence ADRGLTTRPGSGLTNIKTEEISEVNLDAEF [SEQ ID NO: 9], and the cleavage site is between residues 26 and 27.

These synthetic APP substrates are incubated in the presence of beta-secretase under conditions sufficient to result in beta-secretase mediated cleavage of the substrate. Comparison of the cleavage results in the presence of the compound inhibitor to control results provides a measure of the compound's inhibitory activity.

#### 10 **Example E**

##### **Inhibition of Beta-Secretase Activity - Cellular Assay**

An exemplary assay for the analysis of inhibition of beta-secretase activity utilizes the human embryonic kidney cell line HEKp293 (ATCC Accession No. CRL-1573) transfected with APP751 containing the naturally occurring double mutation Lys651Met52 to Asn651Leu652 (numbered for APP751), commonly called the Swedish mutation and shown to overproduce A beta (Citron et al., 1992, *Nature* 360:672-674), as described in U.S. Patent No. 5,604,102.

The cells are incubated in the presence/absence of the inhibitory compound (diluted in DMSO) at the desired concentration, generally up to 10 micrograms/ml. At the end of the treatment period, conditioned media is analyzed for beta-secretase activity, for example, by analysis of cleavage fragments. A beta can be analyzed by immunoassay, using specific detection antibodies. The enzymatic activity is measured in the presence and absence of the compound inhibitors to demonstrate specific inhibition of beta-secretase mediated cleavage of APP substrate.

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**Example F****Inhibition of Beta-Secretase in Animal Models of AD**

Various animal models can be used to screen for inhibition of beta-secretase activity. Examples of animal models useful in the invention include, but are not limited to, mouse, guinea pig, dog, and the like. The animals used can be wild type, transgenic, or knockout models. In addition, mammalian models can express mutations in APP, such as APP695-SW and the like described herein. Examples of transgenic non-human mammalian models are described in U.S. Patent Nos. 5,604,102, 5,912,410 and 5,811,633.

PDAPP mice, prepared as described in Games et al., 1995, *Nature* 373:523-527 are useful to analyze *in vivo* suppression of A beta release in the presence of putative inhibitory compounds. As described in U.S. Patent No. 6,191,166, 4 month old PDAPP mice are administered compound formulated in vehicle, such as corn oil. The mice are dosed with compound (1-30 mg/ml; preferably 1-10 mg/ml). After time, e.g., 3-10 hours, the animals are sacrificed, and brains removed for analysis.

Transgenic animals are administered an amount of the compound inhibitor formulated in a carrier suitable for the chosen mode of administration. Control animals are untreated, treated with vehicle, or treated with an inactive compound. Administration can be acute, i.e., single dose or multiple doses in one day, or can be chronic, i.e., dosing is repeated daily for a period of days. Beginning at time 0, brain tissue or cerebral fluid is obtained from selected animals and analyzed for the presence of APP cleavage peptides, including A beta, for example, by immunoassay using specific antibodies for A beta detection. At the end of the test period, animals are sacrificed and brain tissue or cerebral fluid is analyzed for the presence of A beta and/or beta-amyloid plaques. The tissue is also analyzed for necrosis.

Animals administered the compound inhibitors of the invention are expected to demonstrate reduced A beta in brain tissues or cerebral fluids and reduced beta amyloid plaques in brain tissue, as compared with non-treated controls.

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**Example G****Inhibition of A Beta Production in Human Subjects**

Subjects suffering from Alzheimer's Disease (AD) demonstrate an increased amount of A beta in the brain. AD subjects are administered an amount of the compound inhibitor formulated in a carrier suitable for the chosen mode of administration. Administration is repeated daily for the duration of the test period. Beginning on day 0, cognitive and memory tests are performed, for example, once per month.

Subjects administered the compound inhibitors are expected to demonstrate slowing or stabilization of disease progression as analyzed by changes in one or more of the following disease parameters: A beta present in CSF or plasma; brain or hippocampal volume; A beta deposits in the brain; amyloid plaque in the brain; and scores for cognitive and memory function, as compared with control, non-treated subjects.

**Example H****Prevention of A Beta Production in Subjects at Risk for AD**

Subjects predisposed or at risk for developing AD are identified either by recognition of a familial inheritance pattern, for example, presence of the Swedish Mutation, and/or by monitoring diagnostic parameters. Subjects identified as predisposed or at risk for developing AD are administered an amount of the compound inhibitor formulated in a carrier suitable for the chosen mode of administration. Administration is repeated daily for the duration of the test period.

Beginning on day 0, cognitive and memory tests are performed, for example, once per month.

Subjects administered the compound inhibitors are expected to demonstrate slowing or stabilization of disease progression as analyzed by changes in one or more of the following disease parameters: A beta present in CSF or plasma; brain or hippocampal volume; amyloid plaque in the brain; and scores for cognitive and memory function, as compared with control, non-treated subjects.

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